DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR FISCAL YEAR 2022

WEDNESDAY, MAY 26, 2021

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

The subcommittee met at 10:01 a.m., in room SD–562, Dirksen Senate Office Building, Hon. Patty Murray (chairwoman) presiding.

Present: Senators Murray, Reed, Shaheen, Schatz, Baldwin, Murphy, Manchin, Blunt, Shelby, Graham, Moran, Kennedy, Hyde-Smith, Braun, and Rubio.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

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

ACCOMPANIED BY:

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

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OPENING STATEMENT OF SENATOR PATTY MURRAY

Senator MURRAY. Good morning. The Senate Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies will please come to order.

Today, we are having a hearing on the Biden Administration's fiscal year 2022 Budget Request for the National Institutes of Health. Senator Blunt and I will each have an opening statement, and then I will introduce our witnesses. And after the witness testimony, Senators will each have 5 minutes for a round of questions.

Before we begin, I do want to walk through the COVID–19 safety protocols that are in place today. And again, I really want to thank

all of our clerks and everyone who has really worked hard to get this set up and help us all stay safe and healthy. So, thank you to them.

For today, we are going to be conducting this hearing following similar COVID protocols to what we have used in the past. Committee members are seated at least 6 feet apart. Some Senators are participating by videoconference. However, I do expect that this will be our final hybrid hearing, and we will be able to return to regular, in-person hearings at our next hearing.

Consistent with CDC guidance, those who are fully vaccinated do not need to wear a mask, though they may still choose to do so. And while we are unable to have the hearing fully open to the public or media for in-person attendance, live video is available on our committee website. And if you are in need of accommodations, including closed captioning, you can reach out to the committee or the Office of Congressional Accessibility Services.

As of today, almost half of U.S. adults are fully vaccinated. And while we have a lot of work left yet to do to reach communities who still cannot get vaccines and reassure people who still have many questions about them, we can see the light at the end of the tunnel. And, I really want to thank all of our witnesses, especially Dr. Collins and Dr. Fauci, for putting in long hours and putting science first.

Where we are at today is a testament to the tireless work scientists at NIH have been doing to study this disease and how we can best fight it, and oversee clinical trials for vaccines and therapeutics and more, to ensure they are safe and effective. And, of course, as our witnesses know, our historically fast progress in fighting COVID–19 and developing safe and effective vaccines was actually years in the making.

The pace of discovery we have seen this past year was made possible by research into mRNA vaccines we funded in response to Ebola and other viruses, and biomedical research enterprise that has been built over decades to become one of the most cutting edge in the world.

This should be an important reminder when it comes to biomedical research. You can never fully predict how the discoveries of today will prepare you for the challenges of tomorrow. That is why you have to build the robust research enterprise and recruit diverse, world class talent, and make sure scientists can do their work free from political interference.

And President Biden's budget, which proposes over $40 billion for NIH (National Institutes of Health), the largest increase in the agency's history, will go a long ways towards making sure we can continue to prioritize this. This budget will reinforce our work to fight COVID–19, along with many other diseases and disorders that threaten families in my home State of Washington, or Missouri, or across the Country.

It includes funding to improve treatments for addiction and substance use disorders, and funding to aid the fight against cancer, Alzheimer's disease, and rare diseases families across the Country are grappling with.

President Biden's budget request will also fund research to help us study the health effects of climate change, which may be in-

creasing the number of infectious disease outbreaks; identify solutions to gun violence, which continues to claim tens of thousands of lives each year in this Country; and root out the health inequities in our Country, which are undermining the health of people of color, people with disabilities, rural communities, those paid low incomes, and more.

The President has also proposed $6.5 billion for a new initiative—the Advanced Research Projects Agency for Health. Like the defense initiative it is inspired by, ARPA–H is envisioned as breaking the mold for how cutting-edge research is conducted, speeding up the development of medical treatments by funding innovative projects. I am interested to hear more about how it can add to NIH's work and operate as something truly distinct from its other traditional, biomedical research programs.

Of course, at the end of the day, innovation is not just driven by new programs and new investments. It is driven by people, which is why with as much as we invest in NIH each year, and as important as its work to its families, our families, we cannot afford to have this agency's potential limited or its success threatened by bias, discrimination, harassment, or assault in the workplace.

Unfortunately, we know that in the biomedical research community, the prevalence of researchers of color is too low, and the prevalence of sexual harassment is too high. These are real problems with real consequences for biomedical research and the people who do the lifesaving work we are all benefitting from today.

I commend NIH for the efforts it has taken on both of these fronts so far. NIH has done work to examine barriers to diversity among its researcher ranks and how its own practices have reinforced structural biases that allow discrimination to persist. But, more work remains to tear down barriers and create lasting change.

And when it comes to sexual assault, Director Collins, I am glad you have taken some forceful action to address the problem among the NIH workforce, but NIH must do more to use its enormous influence with the research community to enforce change in the Nation's universities and research institutions. I expect NIH to continue building on its efforts so far to remove racism, discrimination, and harassment from research, and I will continue to follow up on that progress.

Finally, as proud as we all are of our Nation's biomedical research institutions, we do not invest billions of dollars in biomedical research out of pride, nor do we invest in them to help pharmaceutical companies make astronomical profits. We do it to bring new treatments, cures, and hope to people across the Country and across the world. It is important that we never lose sight of this because even the most brilliant miracle cure can only save people if they can actually get it.

Just as I hope to work with my colleagues on both sides of the aisle to make lifesaving investments in biomedical research like those proposed in the President's budget, I also hope we can work together to bring down the cost of healthcare, especially for prescription drugs; keep working towards universal health coverage; and bring the cures we are investing in to the families who need them.

With that, I will turn it over to Senator Blunt for his remarks.

STATEMENT OF SENATOR ROY BLUNT

Senator BLUNT. Well, thank you, Chair Murray. I appreciate having this hearing today and appreciate being able, again, to start this process with you as we did last week on our first hearing.

I am certainly glad that Dr. Collins and the Institute directors are here with us today. I think two of the directors are testifying before the committee for the first time, and, so, welcome to the two of you. And this is a helpful relationship for us, and hopefully for you.

Certainly, the challenges we have faced over the past year have been unanticipated and significant. I think the global pandemic reinforced the importance of the National Institutes of Health. In less than a year, NIH was able to take this novel coronavirus and help develop two FDA (Food and Drug Administration)-authorized vaccines, two FDA-authorized therapeutics, and 16 rapid diagnostic tests, including the first FDA-authorized point-of-care diagnostic test for COVID–19 to combat its spread and its effects.

A year ago, when we would have had a similar discussion, one of the big topics would be, why can't we get enough tests? NIH stepped up and really played a big role in seeing that we had enough tests. We have not heard that discussion for a long time. And that does not mean that millions of tests are not being taken every day. It just means we figured out at this committee and NIH to be part of meeting that need.

It was revolutionary to watch NIH work, but it did not just happen. In a time of crisis, during shutdowns, during social distancing, dealing with a disease that has never been seen before, the system and its nationwide grantees were able to use their expertise and infrastructure to, again, develop tests, treatments, and vaccines. Our research infrastructure was tested like never before and, in my opinion, it succeeded in remarkable ways.

I believe there are really three reasons for that. First, in the past 6 years, this committee and the Congress, in a bicameral, bipartisan way have prioritized and invested in NIH. Within that 6-year timeframe, funding for medical research increased by almost $13 billion, or nearly 43 percent over that 6 years after a decade at virtually level funding. This investment encouraged young scientists, young researchers, and mid-career researchers that were leaving the field before that to stay in the field. And, with your insistence, Dr. Collins, some of that money every time was set aside to be sure that it was going to first-time grantees.

We were able to shore up the research infrastructure across the Country and provide research into mRNA, an idea that had never produced a vaccine before and, of course, became the foundation for the two principal vaccines that were developed very much with the involvement of NIH.

Our ability to pivot so quickly and so successfully to fighting COVID–19 could not have been accomplished had we stayed at the funding levels we were at 7 years ago. The buying power was not where it needed to be. Young researchers were leaving the field. Tough budgetary decisions meant that people were not only getting their applications rejected at significant levels; they just, frankly,

stopped making a lot of applications. That is not your problem, by the way, today.

Second, at the height of the pandemic, Congress gave the Department of Health and Human Services significant funding and flexibility to create Operation Warp Speed. It was successful in developing two FDA-authorized COVID–19 vaccines and commercializing another with the help of NIH because we united in our effort to make that happen.

One of the things we did was to really invest in vaccines that we did not think were certain to work, but thought were likely to work, and that meant that vaccines were available when they got FDA authorization rather than months after they got FDA approval. Because of that, fully half of all adults have been vaccinated now in the United States as we work toward a bigger number than that.

We pushed private industry and worked with private industry in ways we had not before. I have said at the time, one way to win the horse race is to bet on all the horses. And I think to a great extent we did in the vaccine effort, bet on all the horses we thought had a chance to finish the race, and it made a difference.

Finally, one of the most important lessons learned from the pandemic is the value of having the Federal Government, on occasion, as a more active partner in research and development instead of just a sponsor. The ambitious speed and goals that pushed private companies to research, develop, and manufacture a COVID–19 vaccine, along with what we did in testing, really created the kind of breakthroughs we needed.

RADx and Warp Speed, I think put us in a different place than we would have been 2 years ago in thinking about how we can look at some of our research efforts in another way. That is why I want to work with the Administration to support the ARPA–H initiative. This will be a new institute, or is proposed to be a new institute, and I think that is what should be the case. They will have the flexibility and tools necessary to both nimbly and innovatively respond to both the next pandemic and also some of the big health issues we face today.

This is a critical moment in a rapidly changing healthcare world. Finding those things that the kind of Warp Speed, Shark Tank, RADx relationship could enhance in cancer, in Alzheimer's, in every disease where there is an opportunity; where we see that moment and know that this is something that does not necessarily call for a 5-year research grant, but some sort of partnership different than that that moves toward a real conclusion sooner than we might otherwise be able to do that.

ARPA–H should not do what the other institutes do, but it should do what the other institutes cannot do in a crosscutting way that goes throughout the institutes, looking for opportunities, frankly, in the other institutes where there is a breakthrough moment that we could look at differently. I think we can help fill gaps here that otherwise would not be filled and look forward to that discussion.

Now, also, as someone working with Senator Murray for the last 6 years to increase the funding and the focus in what NIH has been doing, we clearly want to be sure that this somehow does not

take away from the solid research that proves so effective in getting us ready for what we just saw.

So, Dr. Collins, I look forward to working with you and Chair Murray and the Administration in making ARPA–H a reality. I think the moment is ready for that. I think because of what has happened in the last 2 years, NIH is ready for that, and look forward to the discussion today.

[The statement follows:]

PREPARED STATEMENT OF SENATOR ROY BLUNT

Thank you, Chair Murray. I appreciate Dr. Collins and the other Institute Directors for being here today.

The challenges we have faced over the past year in a global pandemic reinforced the importance of the National Institutes of Health.

In less than a year, NIH was able to take this novel coronavirus and develop two FDA-authorized vaccines, two FDA-authorized therapeutics, and 16 rapid diagnostic tests, including the first FDA-authorized point-of-care diagnostic test for COVID–19, to combat its spread and effects.

This was revolutionary, and it didn't happen without decades of preparation.

In a time of crisis, during shutdowns and social distancing, for a disease never seen before, the NIH and their nationwide system of grantees were able to use their expertise and infrastructure to develop tests, treatments, and vaccines for COVID–19. Our research infrastructure was tested like never before, and it succeeded. And I believe there were three key reasons behind this success.

First, for the past six years, this Committee and Congress have prioritized and invested in NIH. Within this timeframe, funding for medical research increased by $12.85 billion, or nearly 43 percent, after having spent the previous decade at virtually level funding.

This investment encouraged young and mid-career scientists in the field, who often have the most novel and innovative research ideas, shored-up the research infrastructure across the country, and provided research into mRNA, which is the foundation for two of the COVID–19 vaccines.

Our ability to pivot so quickly and so successfully to fighting COVID–19 could not have been accomplished had this Committee let NIH funding stagnate for another decade, dragging down its buying power, and letting young researchers leave the field. Making the tough budgetary decisions necessary to prioritize the NIH paid off.

Second, at the height of the pandemic, Congress gave the Department of Health and Human Services significant funding and flexibility to create Operation Warp Speed. It was successful in developing two FDA-authorized COVID–19 vaccines and commercializing another, with the help of NIH, because it united the federal government, private companies, and researchers around a common goal.

The reason that we have been able to fully vaccinate half of all US adults is because there was a deliberate strategy in the last Administration to focus and provide funding for any COVID–19 vaccine or therapeutic that had the likelihood to work. We took financial risks to manufacture vaccines as the development process was still underway.

We pushed private industry to innovate their own approaches. And we forever changed the drug approval process. As I have said before, the way to win a horse race is to bet on all the horses. That is what this Committee and the previous Administration did.

Finally, one of the most important lessons learned from the pandemic is the value of having the Federal Government become a more active partner in research and development, instead of just a sponsor.

The ambitious speed and goals that pushed private companies to research, develop, and manufacture a COVID–19 vaccine through Operation Warp Speed demonstrated that active collaboration in public-private partnerships, in conjunction with significant funding, are game changers in creating scientific breakthroughs.

Now we must learn from these lessons. There is an opportunity to build upon Operation Warp Speed and NIH's RADx diagnostic testing program to leverage public-private partnerships to dramatically accelerate the development and approval of new treatments and technologies. What two years ago would have been termed risky and financially unpalatable now is possible.

And that is why I want to work with this Administration to support the ARPA–H initiative. This will be a new Institute that will have flexibility and tools necessary to nimbly and innovatively respond to both the next pandemic and also to

some of the biggest health issues Americans face today, like cancer and Alzheimer's disease.

ARPA–H should do what other NIH Institutes cannot. It needs to be cross-cutting throughout all the NIH Institutes and collaborative both internally with NIH and HHS and externally with partners. It needs to be innovative. And it should help fill the gaps we clearly saw during the pandemic between basic science and commercialization of COVID–19 vaccines and therapeutics.

Simply put, there are aspects of NIH research that could move much faster outside the traditional NIH grant cycle. The NIH peer review process is the gold standard, but we also need to recognize that it doesn't work for all research at all times.

I look forward to working with you, Dr. Collins, and you, Chair Murray, on making ARPA–H a reality.

It will take collaboration between the Administration, NIH, and Congress. But as we work toward a new Institute to accelerate the application and implementation of health discoveries, we must make sure that basic science is not abandoned. ARPA–H should not be the shiny new toy we all focus on, especially not to the detriment of the NIH research community as a whole.

If there is one lesson we must take from this pandemic, it is that our nation's success depends on the medical research infrastructure across this country supported by the NIH. Now is not the time to abandon it. Now is the time to make it even stronger.

Thank you.

Senator MURRAY. Thank you very much, Senator Blunt.

I will now introduce our witnesses.

Dr. Francis Collins is the director for the National Institutes of Health.

Dr. Diana Bianchi is the director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Dr. Anthony Fauci is the director of the National Institute of Allergy and Infectious Diseases.

Joining us virtually is Dr. Gary Gibbons. He is the director of the National Heart, Lung and Blood Institute.

Dr. Eliseo Pérez-Stable is the director of the National Institute on Minority Health and Health Disparities.

Dr. Ned Sharpless is the director of the National Cancer Institute.

And, finally, Dr. Bruce Tromberg is the director of the National Institute of Biomedical Imaging and Bioengineering.

So, Dr. Collins, we will turn to you for your opening remarks.

SUMMARY STATEMENT OF DR. FRANCIS S. COLLINS

Dr. COLLINS. Thank you, Chair Murray and Ranking Member Blunt and distinguished members of the subcommittee. I am honored to be here today with my colleagues representing the National Institutes of Health, the NIH.

I could spend hours describing the exciting work the President's budget is proposing for NIH, including major investments to address impacts of the COVID–19 pandemic, reduce health disparities in maternal mortality, improve mental health, broaden approaches to pain and opioid addiction, and establish a bold, new agency within NIH called ARPA–H.

But, in our brief time together, it is also important to emphasize how steady funding increases that you have provided to NIH, starting well before the pandemic, made it possible for NIH to meet the challenges of the pandemic and to prepare for what comes next.

Often at these hearings, I share a story of a patient whose life has been saved by NIH research, but in this uniquely challenging year, it is hard to single out any one person. In fact, all of the more

than 160 million Americans who have received COVID–19 vaccines as of today are success stories made possible by the sustained investment that this committee made years ago to basic biomedical research.

The road to these mRNA vaccines actually started back in the 1960s when the function of messenger RNA was first understood. These messengers carry instructions from the cell's DNA manual to produce the proteins that do the work. Now, for vaccines, we knew that certain proteins, like the spike proteins on the coronavirus, could spur an immune response. But, might it be safer and just as effective to use the RNA, the codes for those spike proteins, to instruct the patient's body to produce them? And it took a lot of obstacles to surmount to get there over more than 20 years, but we are blown away by how well it works.

In parallel, other NIH-supported scientists, including some at our own Vaccine Research Center, learned that locking those spike proteins into the right configuration could make an even better vaccine. So, when COVID hit, we knew exactly what to do, but we needed the help of the American people enrolling in clinical trials to finish the job. To facilitate that, NIH opened a dialogue with communities disproportionately affected by COVID to ensure that they had access to the vaccine trials.

The Community Engagement Alliance, or CEAL, c-e-a-l, Initiative built on some existing, long-term partnerships with trusted leaders in underserved communities to engage directly on trial enrollment, and later with hesitant individuals on issues related to vaccine safety and efficacy.

We were able to use the enrollment techniques we learned in the large, longitudinal studies, such as All of Us, that you have championed. The result is that all Americans can look at the major vaccine trials and see that people like them were included.

While the vaccines were in early trials, the world was clambering for rapid diagnostics to understand and manage our risks. Members of this committee, most notably Senator Blunt, asked what NIH could do to ramp up innovation. And thanks to your support, and using a novel Shark Tank approach, NIH took on a new role as a venture capitalist through the Rapid Acceleration of Diagnostics, or RADx program.

Today, there are 33 novel testing platforms helping perform just today, millions of tests daily, due to RADx. This program demonstrated the remarkable innovations that are possible when NIH brings together experts in engineering, business, and manufacturing to fund big ideas.

Now, the President's budget proposes a major investment to build on this momentum the Advanced Research Projects Agency for Health, or ARPA–H. This new agency within NIH will catalyze novel strategies to speed transformational and innovative ideas, ideas such as simple blood tests to detect free-floating DNA or protein markers that signal a cancer is growing somewhere in the body; a micro needle patch that delivers a vaccine to hard-to-reach communities in the mail; using an innovation funnel to recruit, test, and scale up new technologies for ambulatory blood pressure measurement with the potential to transform the management of hypertension.

These are just a few of the bold ideas that ARPA–H could tackle, but they are not science fiction. With standard approaches, well, they might happen in a decade or two. With ARPA–H, we believe it could take half that time.

The President believes that with your help, we can learn from the lessons of pandemic and transfer this scientific momentum into big improvements in the health of all Americans. I do, too.

My colleagues and I would be pleased to answer your questions.

[The statement follows:]

PREPARED STATEMENT OF FRANCIS S. COLLINS, M.D., PH.D., DIANA W. BIANCHI, M.D., ANTHONY S. FAUCI, M.D., GARY H. GIBBONS, M.D., ELISEO J. PÉREZ-STABLE, M.D., NORMAN E. SHARPLESS, M.D., AND BRUCE J. TROMBERG, PH.D.

Good morning, Chairwoman Murray, Ranking Member Blunt, 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.

First, I want to thank this Subcommittee for your commitment to NIH, which allowed the biomedical research enterprise to respond quickly to the greatest public health crisis in our generation over the past year. We mounted vigorous research efforts to understand the viral biology and pathogenesis of the coronavirus disease 2019 (COVID–19), develop vaccines in record time, support and commercialize diagnostics at the point of care, and test therapeutics for both outpatient and inpatient settings. This work is far from finished.

The President's Discretionary Request proposes budget authority of $51 billion for NIH in fiscal year (FY) 2022. The Biden Administration places great emphasis on research and development in general. At NIH in particular, the Request proposes to build on the successes of pandemic era research and to put the research enterprise to work on some of our Nation's most persistent and perplexing health challenges, including cancer, Alzheimer's disease, opioid use disorder, health disparities, maternal mortality, HIV/AIDS, gun violence, climate change, and other areas with major implications for our Nation's health.

First and foremost, the President's Request proposes $6.5 billion to establish the Advanced Research Projects Agency for Health—ARPA–H to drive transformational innovation in health research and speed application and implementation of health breakthroughs. ARPA–H will tackle bold challenges requiring large scale, cross-sector coordination, employing a non-traditional and nimble approach to high risk research, modeled after DARPA in the Department of Defense. To achieve this, ARPA–H will invest in emergent opportunities by conducting advanced systematic horizon scans of academic and industry efforts, leveraging novel public-private partnerships, recruiting visionary program managers, and using directive approaches that provide quick funding decisions to support projects that are results-driven and time-limited. Potential areas of transformative research driven by ARPA–H include: the use of the mRNA vaccines to teach the immune system to recognize any of the 50 common genetic mutations that drive cancer; development of a universal vaccine that protects against the 10 most common infectious diseases in a single shot; development of wearable sensors to measure blood pressure accurately 24/7; and leveraging of artificial intelligence technology to advance care for individual patients and improve detection of early predictors of disease.

ARPA–H represents the kind of transformative idea for biomedical research that only comes along once in a long while. Our confidence that NIH is ready has been greatly advanced by our experience in addressing the COVID–19 pandemic—developing vaccines in record time, establishing an unprecedented public-private partnership on therapeutics that has made it possible to test more than a dozen possible therapeutics in rigorous trials, and building a venture capital model for assessing SARS–CoV–2 diagnostic technologies that has yielded millions of daily tests in just months.

But while we begin to imagine a life after COVID–19, we must acknowledge that there are COVID-related impacts that we have yet to understand and address, including the full impact of the pandemic on children. Children were largely spared from COVID–19 but for some children, exposure to the COVID–19 virus led to Multisystem Inflammatory Syndrome in Children (MIS–C), a severe and sometimes fatal inflammation of organs and tissues. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) is leading a multi-institute initiative known as the Collaboration to Assess Risk and Identify loNG-term

outcomes for Children with COVID (CARING for Children with COVID), which will assess both short-term and long-term effects of MIS–C and other severe illness related to COVID–19 in children, including cardiovascular and neurodevelopmental complications.

For many Americans, this pandemic and its related socioeconomic effects have had an overwhelming impact on their mental health. Prior research on disasters and epidemics has shown that in the immediate wake of a traumatic experience, large numbers of affected people report distress, including new or worsening symptoms of depression, anxiety, and insomnia. To aid in mental health recovery from the COVID–19 pandemic, NIH will continue to focus on research in this area. This will be done, in part, by utilizing participants in existing cohort studies, who will be surveyed on the effect of the pandemic and various mitigation measures on their physical and mental health.

The COVID–19 pandemic has brought into sharp focus the dramatic health disparities that exist across the American population. In addition, the Nation has been shaken by the killing of George Floyd and other attacks on people of color, forcing a recognition that our country is still suffering the consequences of centuries of racism. NIH will continue to address these disparities, specifically through research managed by the National Institute on Minority Health and Health Disparities (NIMHD), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Nursing Research (NINR) and the Fogarty International Center (Fogarty).

NIMHD looks to better understand the human biological and behavioral mechanisms and pathways that affect disparity populations, better understand the long-term effects of disasters on health care systems caring for populations with health disparities and research focusing on the societal-level mechanisms and pathways that influence disease risk, resilience, morbidity and mortality. NINR and Fogarty both look to better understand and reduce rural health disparities in low-income counties in the southern United States, support nursing science focused on racial, ethnic, and socioeconomic health disparities, with the goal of closing the gap in health inequities and increase health disparity research in low and middle income countries.

In addition to the core health disparities research, the President's Request puts an additional specific focus on maternal morbidity and mortality (MMM), which disproportionately affect specific racial and ethnic minority populations. Black and American Indian/Alaska Native individuals are two to four times more likely to die from pregnancy-related or pregnancy-associated causes compared to white individuals. Furthermore, Black, Hispanic and Latina Americans, Asian, Pacific Islander, and American Indian/Alaska Native individuals all have higher incidence of severe maternal morbidity (SMM) compared to white individuals. The Implementing a Maternal Health and Pregnancy Outcomes Vision for Everyone (IMPROVE) initiative supports research on how to mitigate preventable MMM, decrease SMM, and promote health equity in maternal health in the United States.

As the climate continues to change, the risks to human health will grow, exacerbating existing health threats and creating new public health challenges. Major scientific assessments document a wide range of human health outcomes associated with climate change. While all Americans will be affected by climate change, underserved populations are disproportionately vulnerable. These populations of concern include children, the elderly, outdoor workers, and those living in disadvantaged communities. NIH is poised to lead new research efforts to investigate the impact of climate on human health, with the goal to understand all aspects of health-related climate vulnerability. Therefore, the President's Request includes a $100 million increase for research on the human health impacts of climate change.

The FY 2022 President's Discretionary Request makes a major additional investment to address the opioid crisis. The crisis of opioid misuse, addiction, and overdose in the United States is a rapidly evolving and urgent public health emergency that has been exacerbated by the coronavirus pandemic. Since the declaration of a public health emergency for COVID, illicit fentanyl use and heroin use have increased, and overdoses in May 2020 were 42 percent higher than in May 2019.

The use of opioids together with stimulants, such as methamphetamine, is increasing; and deaths attributed to using these combinations are likewise increasing. Taking note of these trends, FY 2021 appropriation language expanded allowable use of Helping to End Addiction Long-term (HEAL) funds to include research related to stimulant misuse and addiction. Identifying how opioids and stimulants interact in combination to produce increased toxicity will enhance our ability to develop medications to prevent and treat comorbid opioid and stimulant use disorders and overdoses associated with this combination of drugs.

Finally, I'd like to take a moment to thank this Subcommittee for its recognition over the last two years that America's continuing leadership in biomedical research

requires infrastructure and facilities that are conducive to cutting-edge research. With your support, we will break ground in the near future on a new Surgical, Radiological, and Laboratory Medicine division of our Clinical Center, which will replace severely outdated and deteriorating operating suites and lab space with state-of-the-art facilities. NIH continuously works to ensure that the buildings and infrastructure on its campuses are safe and reliable and that these real property assets evolve in support of science—but NIH's backlog of maintenance and repair is now nearly $2.5 billion. The President's FY 2022 Discretionary Request includes $250 million to make progress on reducing this backlog and requests flexibility for Institutes and Centers to fund construction, repair, and improvement projects.

COVID–19 compelled us to perform a stress test on biomedical research enterprise. The enterprise performed nobly. We found what worked, and also identified barriers we hadn't fully appreciated before, and invented new ways around them. The President's FY 2022 Discretionary Request is a roadmap for how to build on the successes of research, address our gaps, and apply our insights to the most important problems we face as a nation. With your support, the future is filled with opportunity. My colleagues and I look forward to answering your questions.

Senator MURRAY. Thank you very much, Director Collins. I have to say, I have always loved your success stories. They are usually really beautiful. But, I will say, I think many of us in this room are grateful to be your success story this time. So, thank you.

We will now begin our 5-minute rounds of questions, and Dr. Collins, I will start with you.

As you just talked about, the President's budget includes $6.5 billion to create the ARPA–H within NIH that is modeled after DARPA. DARPA is a small, $3.5 billion agency that is composed mostly of program managers and empowered to push the limits of their disciplines and shape some milestone-driven breakthrough technologies in short 3- to 5-year stints.

Given that the nature of NIH's work is different, relying on a peer review system or multi-year grants that is traditionally risk-adverse, where progress is often measured in decades, how do you envision ARPA–H fitting into the NIH ecosystem?

ARPA–H STRUCTURE

Dr. COLLINS. Senator, it is a great question. I think you are right that much of what NIH does requires this kind of careful, deliberative, investigator-initiated, hypothesis-driven research, and that is going to be the mainstay of what we do going forward. That has been the success story of NIH for many decades.

But, there are opportunities, as we have seen happen during COVID, such as the need to develop diagnostics in a hurry, to develop vaccines in a hurry, that are not really amenable to that approach, where you need to have program managers that are empowered to move things swiftly and have the flexibility and the resources to do so. And that is the DARPA model. We have studied that closely, and we do think that there are projects in biomedicine now that would be greatly advantaged by that. That is not the typical peer review process that may take a year from the idea to the first award. With RADx, we made those first awards 5 days after the Congress gave us the budget for it, and that played out really well.

So, we want to incorporate that mindset, and we want to bring on perhaps a hundred of these program managers, give them the opportunity to build the kind of collaborative ventures that include such organizations as small businesses that might otherwise not be likely to write an NIH grant.

Ride herd over these things carefully so that if they are not doing well, they get basically stopped immediately. We expect there will be failures—this is high risk—but identify the areas of greatest opportunity. And every Institute at NIH is now coming forward saying, I have at least five ideas of what I would like to do with ARPA–H that I cannot do right now.

So, this should not be seen as competing with the Institutes. It is going to be a synergistic relationship that will allow us to do things otherwise that would take a very long time.

Senator MURRAY. Okay. Well, you have said that it should be within the office of the director. In that structure, how would decisions be made about what projects to fund?

Dr. COLLINS. So, we will need to hire a director for ARPA–H, who will need to be a visionary person, and the idea is to bring on somebody who is not probably going to be doing this as their long-term career, but maybe for one term, 5 years, with one possible renewal.

That person will be very much engaged then in bringing onboard these very creative program managers who have to make a pitch about what kind of projects they think are worth investing in and convince the director that that is the case. And, then, they are given the flexibilities to go out and find the right partners and see what can happen. But, that is all going to be done in a way that is quite nimble. It is not going to involve our traditional peer review process.

Senator MURRAY. Okay.

STRUCTURAL RACISM AND HEALTH EQUITY

Dr. Pérez-Stable, your career has really focused on improving the health of communities of color and underserved populations. And NIH recently released a $30 million funding opportunity to study the impact of structural racism and discrimination in order to promote health equity and eliminate health disparities. Can you talk to us a little bit about what more can NIH, and particularly NIMHD (National Institute on Minority Health and Health Disparities), be doing to address those issues, and what would be the benefit of making additional investments?

Dr. PÉREZ-STABLE. Thank you, Senator Murray, for that question. So, first of all, we had to recognize that structural racism could be operationalized as a research construct and not just an organizational construct, and we went through a workshop and scientific reflection on this. I think the moment earlier this year for all of the NIH Institutes and Centers agreed that this was an area that we needed to move on and advance more quickly in the research side. And, so, we had a commitment from all the institutes that do this, although NIMHD was leading it from the beginning.

We believe that two areas are susceptible for improvement. One would be the healthcare setting, where I think through interventions at the structural, as well as the clinician and the patient level will help. And, also, in promoting healthy communities so that we can have easier access to green space, to healthy food, accessible healthcare in community health centers.

These are two areas that we believe are susceptible for improvement, although we will depend on our scientific community to pro-

mote and submit ideas that will be reviewed and hopefully funded within fiscal year 2022.

Senator MURRAY. Okay. Thank you very much. I look forward to working with you and hearing more about that.

Senator Blunt.

Senator BLUNT. Thank you, Chairman.

ARPA–H FUNDING LEVEL

Dr. Collins, on the ARPA–H budget request, $6.5 billion, one part of the question will be, how do you think that number was arrived at, and is that a realistic number to commit in year one?

And two, our concern would also be that we do not get in a position that—we have already given NIH $6.5 billion and level fund everything else. I do like the President's $2.5 billion. I am sure you could figure out how to spend more than that in the other institutes. That is pretty close to the average of the last 6 years from our committee. I would certainly like to stay at least at that level.

But, how do you think those two numbers compete with each other? And how do you feel about actually being able to commit $6.5 billion in that first fiscal year of ARPA–H?

Dr. COLLINS. That is a great question, Senator, and we have thought a lot about it. I am pleased the President's budget proposes that this would be 3-year money because, obviously, you are going to start from a standing start whenever the budget actually gets approved for fiscal year 2022. We hope that will be September 30th, right? Well, it might not be. So, at any rate, we would then really be benefitted by being able in that first year to stretch those dollars over a little bit.

I do think we could, with a hundred program managers, readily come up with a number of projects that would fit within that envelope on an annual basis. But, I hear what you are saying about a concern because I have heard it also that this might in some way compromise the interest of the Institutes. I guess I would look at it a different way, though.

As I said earlier, every one of the Institutes is coming forward with great ideas about how they would like to use ARPA–H. They think of this as an augmentation of their capabilities, not a subtraction. And, so, they will be feeding ideas into this and have a lot to do about how those are chosen. So, even though the base number that is being proposed, $2.5 billion for the ICs (NIH Institutes and Centers), may sound like a sort of average one, in terms of the science they can do, ARPA–H is going to add to that.

Senator BLUNT. All right. Thank you.

ARPA–H AND CANCER RESEARCH

Well, Dr. Sharpless, one of the things the President, of course, talks about in this issue, in this topic, is more rapidly moving toward ending cancer. Obviously, we want to do that. We also want to make the point that that is not the only thing that ARPA–H would be focused on, nor would it just be cancer or Alzheimer's. But, on that topic, how do you envision the ARPA–H role in cancer research and what might you be able to do with ARPA–H that you are not able to do in the traditional restraints of the National Cancer Institute?

Dr. SHARPLESS. Thank you for the question, Senator Blunt. It is great to be testifying in front of this committee again. Good to see you virtually, at least, today.

Yes, as the President has said, ending cancer as we know it is a top domestic priority for this Administration. We are obviously, the cancer research community, is galvanized by this notion and very excited.

I think, as you know, the National Cancer Institute does some things really well. You know, we fund basic foundational science very well. We can do clinical trials quite well. But, there are some areas where we are challenged, where we have struggles, and I think the scale and nimbleness and ability to interact with industry is very appealing about ARPA–H for certain kinds of cancer projects.

I think a good example of that is this blood-based cancer detector technology that Dr. Collins mentioned in his opening statement where you can, you know, find cancers at a very early stage in otherwise asymptomatic, healthy people, and that could have a profound effect on cancer mortality.

So, you know, getting up a huge trial of that technology as quickly as possible is the kind of thing that I think would be a good fit for ARPA–H.

Senator BLUNT. Okay. Thank you, Dr. Sharpless.

RADX PARTNERSHIPS

Dr. Tromberg, let me see if I can get one more question in. I think what you were part of at RADx is one of the reasons that gives me real optimism about new kinds of relationships that we might develop at ARPA–H. But, would you talk just a little bit about RADx and how that partnership continued right through the entire process of these companies that you were choosing to invest money with, going ahead and making the first home-based test, and I think producing well over two million tests every day now, in addition to the tests that would have come through the regular process?

Dr. TROMBERG. Yes. Thank you so much, Senator Blunt, and thank you for your question and for your generous support of the RADx program.

The bioengineering-technology community has formed partnerships all across the government. That has included working with BARDA, FDA, DOD (Department of Defense), CDC (Centers for Disease Control and Prevention), HHS (Department of Health and Human Services), and the White House Testing Board. More than 900 scientists are working across government, academia, and the private sector in a very unique way to make this work.

And, as you have mentioned, if we fast-forward to now, about 1 year later, we now have 33 RADx-supported companies that have increased the Nation's testing capacity by more than 300 million new tests, and there have been 23 new FDA authorizations. And we have really changed the dialogue from laboratory testing of symptomatic folks to over-the-counter, widely available tests, point-of-care tests that are accessible to all. Greater choice and greater capabilities. And this has really happened because of all of these partnerships that we formed, the accelerated innovation.

We have brought out new technologies. About 20 percent of our portfolio actually—not many people know about—has been based in nanoscience and nanotechnology.

Senator BLUNT. Good.

Dr. TROMBERG. So it has been a tremendous surge for innovation.

Senator BLUNT. Thank you, Doctor.

Thank you, Chairman.

Senator MURRAY. Yes. Senator Reed.

Senator REED. Thank you very much.

I want to welcome all the panelists and thank them for their distinguished service to the Nation, particularly during this difficult and challenging COVID pandemic.

Dr. Collins, one of the things that is becoming unfortunately and painfully obvious is the increase in suicides, and this is very disturbing. And we are concerned, also, about the impact of COVID–19 on accelerating, perhaps, that phenomenon.

SUICIDE PREVENTION

So, the question I would have is, what research is NIH doing on suicide prevention so that we can recognize the warning signs, better communicate with friends and family, and also give healthcare providers more insight? I am told that many suicide victims visit emergency rooms frequently before their suicide and those signs are not picked up. So, your comments would be appreciated.

Dr. COLLINS. Well, I appreciate the question, Senator, and it is a source of great concern and obviously great heartache for the way in which this is taking a toll amongst people across our Nation, and certainly at a time where mental health issues have been even further heightened by all the stresses of COVID–19. One can see this also becoming even more of a threat to people who have lost hope.

NIH is deeply engaged in trying to understand ways to prevent this terrible outcome, and the National Institute of Mental Health has in fact invested in a number of new initiatives as a result of that concern.

One that I would point to that has turned out to be a pretty encouraging development is the recognition that the drug Ketamine, which is used in anesthesia and sometimes used as a party drug, unfortunately. It also turns out to have benefits for people with serious depression, including people with suicidal ideation. Now approved by FDA, and the drug Esketamine, this is now available and it is being used in those acute situations of acute suicidal threat.

You also mentioned that many people who are on the brink do end up visiting healthcare facilities. We have worked hard to try to make sure that this idea of having a screening tool that was used in emergency rooms for individuals who are there, even if they do not appear to be there for psychiatric reasons, gets used to identify, particularly with adolescents, whether they might be in a situation of contemplating self-harm.

On top of that, certainly NIMH is investigating other means of treating depression, and also thinking hard about other interventions that might be beneficial here in terms of cognitive behavioral therapy combined with pharmacotherapy to try to assist those indi-

viduals who are in this difficult place. But, it is a terribly difficult problem.

I will say, it is interesting, but it is not necessarily that encouraging, the actual suicide rate, as best we know, in the course of the last year has not gone up. It has actually gone down slightly, and that has tended to be the case in national crises before. But, what I worry about is what happens when we seem to be getting past the crisis, is there a pent up backup there that might in fact result in an even greater risk in the coming months.

I would be glad to give you more information. I am sure Dr. Gordon would, as well, in terms of all the things that we are doing.

Senator REED. Thank you very much.

LONG COVID

Very quick question to both—to Dr. Fauci. The long haul COVID–19 is beginning to trouble a lot of people. They never seem to be able to recover from it and recurrences. What attention are we paying to that issue?

Dr. FAUCI. Thank you for that question, Senator. We are paying a considerable amount of attention to it. In fact, we have a program to the tune of $1.15 billion, looking at developing cohorts of individuals so that we can study them for the incidence, the prevalence, underlying pathogenesis, and, if possible, if we can find this out, anything that we can do from an intervention. So, the NIH is taking this very seriously. Thank you.

Senator REED. Thank you very much.

I have to commend Dr. Sharpless for his efforts on childhood cancer. I was teamed up with Senator Capito. We passed the Childhood Cancer STAR Act. We have been funding it, thanks to the Chairwoman, at $30 million a year, and I want to commend NIH on its renewed emphasis on childhood cancer, not only treatments, but also gathering data about these victims as they age so that we can see if there is any interventions that we can use later on. So, thank you, Dr. Sharpless, and thank you, panelists. Thank you very much.

Senator MURRAY. Thank you. Senator Graham.

Senator GRAHAM. Thank you, Madam Chairman.

VACCINE DEVELOPMENT

The vaccine, developing the vaccine as fast as we did, what is your biggest takeaway, Dr. Collins? How did we do that? And how can we do it again if we have to?

Dr. COLLINS. It is really important to look and see that this was built upon decades of research in basic science that many people might have said would not probably end up being as relevant as it turned out to be.

Senator GRAHAM. So, all of our money in the past paid off here, right?

Dr. COLLINS. Absolutely. This committee, and then the Congress, especially over the course of the last 6 years where you have increased the NIH support by 40 percent, has made it possible for us to do a lot of things that otherwise we would still not have been able to start. So, yes, it is all built upon that foundation.

Senator GRAHAM. Do you feel like the budget request being made is enough to continue to build on what we have done?

Dr. COLLINS. I am very supportive of the President's budget request, as you might expect I would be. And I am particularly excited about this new proposal of ARPA–H, a new component of NIH that would give us kind of a DARPA attitude that we could bring to projects that are waiting for that kind of opportunity.

Senator GRAHAM. Well, I just hope we can memorialize what we did to get the vaccine out so quickly.

GLOBAL VACCINE DISTRIBUTION

The developing world—Dr. Fauci, one thing I worry about is getting the vaccine out into the developing world, particularly Africa. What can we do better in that regard? And why should we?

Dr. FAUCI. Well, first of all, the answer to your second question, which is very relevant, Senator, is why should we? And the reason we should is that a global pandemic requires a global response. And even though, as you well know from the numbers, we are doing extremely well in this Country—we now have over 60 percent of adults having at least one dose, and about almost 50 percent of the adult population in this Country fully vaccinated.

However, even if we get this pandemic under control, which I believe we will within a period of a few months, there is always the danger, when you have viral dynamics in other parts of the world, for the generation of variants that might actually undermine the protectiveness of the vaccines that we have.

Senator GRAHAM. So, it is in America's interest to get the vaccine out to as many people as possible?

Dr. FAUCI. It is absolutely to our interest. I believe—not only do I think it is a humanitarian, moral responsibility, but it is in what I call enlightened self-interest for us to do that.

ORIGIN OF COVID–19

Senator GRAHAM. So, let's talk about our enlightened self-interest for a moment. Has there ever been a pandemic that we know of that started in a laboratory somewhere?

Dr. FAUCI. To our knowledge, no.

Senator GRAHAM. Okay. If this were in fact a breach of protocols in China, if it did come out of a lab, that would be a first for the world; is that right?

Dr. FAUCI. I believe so. There was a situation with an influenza where there was a suspicion that it might have escaped from a laboratory in Russia.

Senator GRAHAM. But this——

Dr. FAUCI. But that has never been validated or confirmed.

Senator GRAHAM. So, have we found any animals that carry COVID–19 that could have been the source of the transmission to humans thus far?

Dr. FAUCI. Thus far, not. I mean, if what you are referring to, Senator, is an intermediate host——

Senator GRAHAM. Right.

Dr. FAUCI [continuing]. We know clearly, for example, with SARS-CoV–1 that a bat virus went into a civet cat, which then

transmitted it into the human population. With MERS, it was a bat to a camel to human.

The intermediate host, if there is one, has not yet been found.

Senator GRAHAM. And we have been looking for that intermediate host; is that fair to say?

Dr. FAUCI. That is fair to say, sir.

Senator GRAHAM. At what point in time would it become more likely it came from the lab if we do not find an intermediate animal host? How much longer?

Dr. FAUCI. I do not think we can give a time element on that, Senator, for the simple reason we still have not yet confirmed what the host is from Ebola. We know that Ebola jumps from an animal reservoir to human, and it has been many years now since the original Ebola outbreaks, and we have not yet nailed that down.

Senator GRAHAM. But we believe that Ebola did not come from a lab?

Dr. FAUCI. Yes.

Senator GRAHAM. Okay.

Dr. FAUCI. Yes.

Senator GRAHAM. So, I guess my point is, who should look, what should we be doing to make sure we find out how it started?

Dr. FAUCI. Right.

Senator GRAHAM. And finally, what should be the consequences to any country, China included that allowed this to happen? What should the world expect of a country if they in fact allowed this virus to come from one of their labs through negligence?

Dr. FAUCI. Well, first of all, when you said, who should, you know, the WHO (World Health Organization) did what they are referring to now as phase one of an investigation, which they felt was not completely adequate, as you know. You have heard me and Dr. Collins and others in the Administration calling for a continuation of the investigation.

I do not think I can comment on your second question. It would have to be the circumstances under which something like that happened, if indeed it happened.

Senator GRAHAM. Well, just very briefly—I know my time is out—I think we should send a clear signal to China—seems to be a source of a lot of pandemics—that if this did occur in the lab, expect something to happen because if we do not, we are just going to reinforce this in the future. And what that something is, I am open-minded to, but I am closed-minded to the idea of doing nothing.

Senator MURRAY. Thank you. Senator Shaheen.

Senator SHAHEEN. Thank you, Madam Chairman, and thank you to you, Dr. Collins, and everyone at NIH for all of your hard work over the last very difficult year and for everything else you are doing.

ARPA–H AND DIABETES

As you are aware, diabetes is one of the most expensive and pervasive of our chronic diseases, and I was pleased that in the authorization at the end—re-authorization at the end of the year, we funded the Special Diabetes Program for 3 years and the work that is being done to advance treatment for Type 1.

But, can you talk about this new ARPA–H agency and to what extent it might be looking at ways to help address diabetes?

Dr. COLLINS. I would love to, and thank you for the question, Senator. This is the hundredth anniversary year of the discovery of insulin, so we have come a long way in those hundred years, but we are not where we really need to be to say we have conquered this one.

ARPA–H, because of its ability to tackle problems in a team-oriented, nimble way, offers us some new opportunities here. Certainly, one of the ones that the Diabetes Institute has been promoting to me of late, sending me ideas, is to transform the way that we actually develop and test therapeutics, shouldn't we at this point be able to come up with therapeutics for diabetes that do not require injections. A totally new approach to how we would treat this disease.

Another one that I am excited about, and I know you have done a lot of encouragement about this, is the artificial pancreas.

Senator SHAHEEN. Right.

Dr. COLLINS. And we have made real progress there, Senator. But, I think we could go a lot faster if we had this coordinated, ARPA X kind of attitude brought to this, both for artificial pancreases that are built on engineering and sort of a feedback loop that gives insulin when it needs to, but maybe even more so the ones that built upon the patient's own stem cells that can be converted into that.

Senator SHAHEEN. And how do we make sure that diabetes is one of those diseases that ARPA–H addresses?

Dr. COLLINS. Well, fortunately, because I think we do have a pretty good budget being proposed here, and diabetes is already mentioned by the President as one of the three areas of interest, I think diabetes is extremely likely to be on the list.

Senator SHAHEEN. Good. Thank you. I am glad to hear that.

COVID–19 VACCINE BOOSTER SHOTS

Dr. Fauci, the question that everybody is asking is, are we going to need a booster shot to complement our COVID vaccination? Do you have any sense of that and what the timing might be for that?

Dr. FAUCI. Two parts to that question, and they are separate but important. I do not anticipate that the durability of the vaccine protection is going to be infinite. It is just not.

Senator SHAHEEN. Right.

Dr. FAUCI. So, I would imagine we will need at some time a booster. What we are figuring out right now is what that interval is going to be. We know from studies following people from the original clinical trials that the protection goes out at least 6 months, and likely a year. But, we do not know right now how long that will be.

So, what we are doing is we are following those cohorts because there is a level of protection that is called a correlate of immunity, and we know that if you are above that level, you are in quite good shape to be protected.

The vaccine itself gives you a level up here. So, how long it takes to start coming back down, we are following it, and two ways of understanding that. One, does, from a lab standpoint, it get below a

certain level; or, do we start seeing a lot more breakthrough infections. Either of those would be a trigger. But, we are following that very carefully.

So, in answer to your first part of your question, I believe we will need a booster. I am not exactly sure when.

Senator SHAHEEN. Thank you.

SUBSTANCE USE DISORDER AND METHAMPHETAMINE RESEARCH

And, Dr. Collins, you may remember that New Hampshire is one of the hardest hit States by the substance use disorder epidemic. And we have seen a decline over the last year because of the pandemic, but we have also seen a replacement of many of those opioids by meth. I think there is a belief among some people who use substances that meth cannot kill you in the same way that an opioid can. And, yet, as I talk to providers, they tell me there are very few treatments that they have available to them to deal with meth.

So, can you tell me what the National Institute on Drug Abuse is doing to try and address the meth piece of substance misuse?

Dr. COLLINS. Absolutely. This is an area of intense interest and concern because what was primarily an opioid crisis is now very much becoming a mixed crisis of opioids and stimulants, and particularly methamphetamine.

I was pleased to see that NIDA (National Institute on Drug Abuse) ran a trial, a phase three trial, on treatment for methamphetamine addiction, which is a combination of injectable Naltrexone and oral Bupropion, and showed benefit. We have not previously had anything to offer to help people who are addicted to meth. That is one step forward.

We also now are running this effort to vaccinate people against methamphetamine. I know that sounds odd, but you could immunize against that compound in a way that it would no longer provide anybody much of a benefit if they decided to use it anyway. We are doing that for heroin and Fentanyl, and we are doing it for meth. But it is very helpful.

Senator SHAHEEN. Excuse me for interrupting. Does that work if people have already been users?

Dr. COLLINS. It will. So, basically, getting your immune system to make an antibody so that in the future, if you encounter that drug, it cannot get to your brain because the antibodies grab onto it.

Senator SHAHEEN. I will have to learn more about that. Thank you. My time is up.

Thank you, Madam Chair.

Senator MURRAY. That is very interesting. Thank you.

Senator Kennedy.

Senator KENNEDY. Thank you, Madam Chairman, Chairwoman.

GAIN-OF-FUNCTION RESEARCH IN CHINA

Dr. Fauci, I believe you have testified that you did not give any money to the Wuhan lab to conduct gain-of-function research. Is that right?

Dr. FAUCI. That is correct.

Senator KENNEDY. How do you know they did not lie to you?

Dr. FAUCI. Excuse me, sir?

Senator KENNEDY. How do you know they did not lie to you and use the money for gain-of-function research anyway?

Dr. FAUCI. Well, we have seen the results of the experiments that were done and that were published and that the viruses that they studied are on public databases now. So, none of that was gain-of-function, so——

Senator KENNEDY. How do you know they did not do the research and not put it on their website?

Dr. FAUCI. There is no way of guaranteeing that, but in our experience with grantees, including Chinese grantees, which we have had interactions with for a very long period of time, they are very competent, trustworthy scientists. I am not talking about anything else in China. I am talking about the scientists. That you would expect that they would abide by the conditions of the grant, which they have done for the years that we have had interactions.

Senator KENNEDY. So you do not think the Chinese would lie to you?

Dr. FAUCI. Well, when you say the Chinese, the Chinese are a rather broad group. I know the scientists that we have dealt with have been trustworthy.

Senator KENNEDY. You think all the scientists have told the truth in terms of the origin of the Wuhan virus and not been influenced by the communist party of China, do you?

Dr. FAUCI. I do not have enough insight into the communist party in China to know the interactions——

Senator KENNEDY. Right.

Dr. FAUCI [continuing]. Between them and the scientists, sir.

Senator KENNEDY. Right. Why are we giving them money in the first place?

Dr. FAUCI. Well, that is a very good question, and thank you for giving me the opportunity to——

Senator KENNEDY. You are welcome.

Dr. FAUCI [continuing]. Answer it. Well, SARS-CoV–1 started in China in Guangdong Province, and it went from a bat to a civet cat to a human.

Senator KENNEDY. Yes, and excuse me, Doc, for interrupting you, but our time is so limited.

Dr. FAUCI. No, no. I am going to be real quick.

Senator KENNEDY. Our time is so limited. Why are we giving money to the labs in China to study virology?

Dr. FAUCI. Well, I am going to give you a rather succinct answer to that, sir.

Senator KENNEDY. I would appreciate that.

Dr. FAUCI. And that is why I was saying the SARS–CoV–1, clearly the bats that have the viruses that are the coronaviruses are in China. As I said a couple of times, it is not in Fairfax County, Virginia or is it in New York. It is in China. So, if you want to show and study importantly the animal-human interface, the viral——

Senator KENNEDY. Because that is where the bats are?

Dr. FAUCI. Yes, the bats.

Senator KENNEDY. Okay. I got it.

Dr. FAUCI. That is where the bats are.

Senator KENNEDY. I want to be sure I understand your testimony. You did not give money to the Wuhan lab to do gain-of-function research?

Dr. FAUCI. That is correct.

Senator KENNEDY. And you believe they did not do gain-of-function research because they told you they did not?

Dr. FAUCI. We have seen the results of the studies that they conducted and they were not gain-of-function.

Senator KENNEDY. Including any private studies?

Dr. FAUCI. Excuse me? Including?

Senator KENNEDY. Any private studies.

Dr. FAUCI. I am not sure what you are getting at, sir.

Senator KENNEDY. Here is what I am getting at. You gave them money and you said, don't do gain-of-function research.

Dr. FAUCI. Correct.

Senator KENNEDY. And they said, we won't?

Dr. FAUCI. Correct.

Senator KENNEDY. And you have no way of knowing whether they did or not except you trust them; is that right?

Dr. FAUCI. Well, we generally always trust the grantee to do what they say, and you look at the results——

Senator KENNEDY. Have you ever had a grantee lie to you?

Dr. FAUCI. I cannot guarantee that a grantee has not lied to us because you never know.

Senator KENNEDY. Yes. Can we agree that if you took President Xi Jinping and turned him upside down and shook him, the World Health Organization would fall out of his pocket?

Dr. FAUCI. I do not think I can answer that question, sir. I am sorry.

Senator KENNEDY. Well, do you think President Xi Jinping has undue influence over the World Health Organization, do you?

Dr. FAUCI. I have no way of knowing the influence of the president of China over the WHO.

Senator KENNEDY. Okay. So you think the WHO is a completely independent body and level playing field, call-it-like-you-see-it, and they really want to get to the bottom of the origin of the virus? Do you believe that?

Dr. FAUCI. My interaction with the WHO and for Dr. Tedros, the Director General, has been one——

Senator KENNEDY. Okay.

Dr. FAUCI [continuing]. That I do believe he is a person of high degree of integrity.

INVESTIGATION INTO ORIGIN OF COVID–19

Senator KENNEDY. I got it. I want to ask one last question. Why did you guys spike—not guys, and ladies. Why did you all spike the prior administration's investigation into the origins of the coronavirus and whether it could have come out of the Wuhan lab?

Dr. FAUCI. Sir, I—we did not spike anything in the prior administration. I am not sure what you mean by spike. But, we have no influence——

Senator KENNEDY. The State Department spiked the prior administration's study.

Dr. FAUCI. But that has nothing to do with the National Institutes of Health.

Senator KENNEDY. So they did not consult with you all?

Dr. FAUCI. They did not.

Senator KENNEDY. Did they consult with you, Dr. Collins?

Dr. COLLINS. I read about it in the press this morning.

Senator KENNEDY. Doc.

Dr. BIANCHI. No.

Senator KENNEDY. They just spiked it without talking to their experts?

You do not want to answer that one, do you?

Dr. COLLINS. I just read about it.

Senator KENNEDY. Thank you, Madam Chair.

Senator MURRAY. Senator Murphy.

Senator MURPHY. Thank you very much, Madam Chair.

Listen, the World Health Organization is the most influential global public health institution in the world, whether my friends like it or not. They have more people and more influence on the ground across the world than anybody else, including the United States.

And, so, if the complaint is that any country, including China, has too much influence, the answer is not for the United States to walk away. The answer is for the United States to double down and make sure that any grievances we have are addressed. Otherwise, the problem for which you are identifying is exacerbated by the United States not being at the table with the WHO.

And while the major donors to that organization certainly have lots of influence, as is the case with every international organization, it is an oversimplification to suggest that they are in the pocket of the Chinese government. China has influence. The United States has influence, as well, so long as we are at the table.

FIREARMS RESEARCH

I have two areas to cover, and the first I wanted to raise with you, Dr. Collins, and that is around the budget request to double the firearm injury and mortality prevention research account. Let me place myself solidly behind that request. Thank you for making it, and I was hoping you might—I apologize if you have gotten a question on this already. I have been listening but in and out a bit.

I am hoping that you might be able to talk a little bit about how you might prioritize that additional funding, especially as it might relate to research on community-based interventions and what works and what does not. And, then, you know, how to make sure that all that information gets out to community partners, folks who are boots on the ground, maybe not the exact set of players that NIH is used to disseminating information to.

Dr. COLLINS. Well, I appreciate the question, and we are enthusiastic about expanding our approach and the amount of funds we can put into research on firearm violence. After all, some 40,000 deaths happen each year from firearms. About 60 percent of those are suicides, which is another topic that came up earlier and is also part of our suicide prevention, is to think about availability of guns.

I think you are right, though, that community approaches are very much ripe for this kind of approach, where you might not just try to change one thing in the community, but see if by coordinating the efforts across multiple different ways in terms of making sure that firearms are not accessible to those people who might misuse them; in terms of particularly adolescent and youth risks of violence and how to intervene.

Maybe we could take an approach that would be more holistic as opposed to trying to fix one thing at a time. With a larger amount of funding here and a community focus, I think we might be able to do that.

Senator MURPHY. The President has proposed, I think, $5 billion to support these community-based interventions. Maybe some of that will be used for assessment and study. But, given the fact that I think we probably can get bipartisan agreement about supporting these investments in prevention, it really would be helpful to use some of this increased funding to assess which ones work and which ones do not.

SOCIAL DETERMINANTS OF HEALTH

Second broad topic, and maybe I will address this both to Dr. Collins and I think, via video, Dr. Pérez-Stable, is on the topic of social determinants of health. And I am just interested to hear a little bit about how we have adjusted research based upon our growing understanding that people's health is dictated by where they live and how much money they make and how close they are to pollution sources.

My sense is that, you know, this is not an easy sort of thing to incorporate into a research community that is sort of used to working in labs and not always used to thinking about how factors outside the body impact health. What have we learned? How has that changed the way that we fund research and encourage applications to come to NIH that might support social determinant research?

Dr. COLLINS. I am going to ask Dr. Pérez-Stable to respond.

Dr. Pérez-Stable: Thank you, Dr. Collins, and thank you, Senator Murphy, for that important question.

At the National Institute on Minority Health and Health Disparities, and throughout NIH, the topics of social determinants of health have always been present. We consider self-identified race and ethnicity and socioeconomic status standard measures to be fundamental factors that influence health in ways that we do not really understand, and that is why we believe that all research with human beings should measure these routinely and follow them.

In addition to these two, though, there are other demographic and individual social determinants of health, of which many are issues related to age and gender, sexual orientation, but then structural social determinants of health that you refer to. Where one lives, plays, and prays, relate to both transportation, housing, and issues around green space and, of course, Internet access, which has become incredibly important, as we know, in the last year. So, we have these fundamentally incorporated into our standard research, and community engagement is really part of everything that we do at NIMHD, and increasingly across the Agency.

Senator MURPHY. Well, thank you for that. I appreciate the new focus you are putting on this. Again, this is an area of potential bipartisan agreement. Senator Sullivan and I have legislation in this space and look forward to working with you on it.

Thank you, Madam Chair.

Senator MURRAY. Thank you. Senator Shelby, are you ready? You want me to——

Senator SHELBY. Yes, I am ready.

Senator MURRAY. Okay.

Senator SHELBY. I just got here. Thank you. I have been at another hearing, and this question may have been asked.

Dr. Collins, always good to see you.

Dr. COLLINS. Likewise.

Senator SHELBY. I agree with a lot of people on this committee that the money we put in to biomedical research benefits mankind, period. Not just our people, but the world, what it has taught.

AUTOIMMUNE RESEARCH BREAKTHROUGHS

Two or three promising areas, biomedical research in the area of autoimmune—that is a big, big topic. You know it better than anybody. What are we—what are the breakthroughs there, the hopes, in two or three of those top areas?

Dr. COLLINS. Well, thank you, Senator. It is good to see you, and I know you are running from one place to another. I am glad you are here.

I just had a wonderful experience yesterday afternoon listening to presentations from a consortium of researchers that we have funded jointly with industry. So, this is called the Accelerating Medicines Partnership, and it is focused on rheumatoid arthritis and lupus.

What they have done is to take this field, which was looking at immunology in a way that was pretty cutting edge 5 years ago, and now completely transformed it by looking at individual immune cells in the synovium of people with rheumatoid arthritis—the lining of the joint—and say, what are you doing there, immune cells, and how does that teach us what the real pathogenesis about——

And for lupus, they are looking at kidney biopsies, because, of course, lupus affects the kidney and that is one of its serious consequences. Same thing, looking at individual cells.

It has completely revamped our understanding of these diseases. We have learned, for instance, that the pericyte, which was just sort of a cell that we thought was hanging out watching in the kidney of somebody with lupus, might be the driver of what is really happening there as far as the immune response. This is not p-a-r-a. This is p-e-r-i, cyte, in case that is not clear. For rheumatoid arthritis, it is the fibroblasts.

And we are so excited about this. We are now planning to expand that same approach to other autoimmune diseases, to psoriasis, to psoriatic arthritis, to Sjogren's Syndrome, and maybe others, as well.

So, you hit me at a great moment. I was so jazzed yesterday to see what has been possible.

Senator SHELBY. All based on bacteria, is it?

Dr. COLLINS. It is all based on this ability to look at single cells, one at a time. We have not really been able to do that until about 5 years ago. We would have to look at thousands of cells and try to infer what was there, and now you can ask each one. And the cell is, after all, the basic unit of all life, and it has been outside of our reach, but not anymore.

Senator SHELBY. What could that do for the autoimmune area?

Dr. COLLINS. I think it can have a huge impact because we now have new targets coming out of this recognition that I think in the next 4 or 5 years, we are going to see a whole new generation of drugs for autoimmune diseases based upon that insight that is just now emerging.

CYSTIC FIBROSIS RESEARCH

Senator SHELBY. I brought this up many a time, but in the area of cystic fibrosis, there have been so many breakthroughs in that area, extending children's lives, adults' lives, and everything. Where are we going there? We have come a long way, but we are not there yet.

Dr. COLLINS. We are not completely there, but, oh, boy, have we come a long way, especially in the last 2 years now with this 30-year effort, and I have been deeply engaged in this having had a role in——

Senator SHELBY. I know.

Dr. COLLINS [continuing]. Discovering the gene back in 1989. And, now, we have this triple drug therapy, which for 90 percent of patients with cystic fibrosis is dramatically beneficial. I get messages almost every week from somebody who was really in tough shape, and now they are back at work; or somebody who was on a transplant list, and now they were taken off of it because their lungs are doing so much better.

But, there is still that 10 percent. This is where I think the gene-editing approach, where you actually figure out how to fix that misspelling of the cystic fibrosis gene in the lungs of somebody who is affected, might be the way to get to 100 percent, and there is a lot of work going on that.

LUPUS RESEARCH

Senator SHELBY. What promises are out there that you have talked about before dealing in lupus, which is an autoimmune disease?

Dr. COLLINS. Well, as I mentioned, we have this ability now to be able to see individual immune cells, what are they up to in lupus, both in the kidney and in other areas, as well. I think that is teaching us some new things about what the real fundamental cause is. And it will tell us that some of the treatments we have been giving, like steroids, are kind of a little bit too much of a sledgehammer, and what we need now is something much more subtle to go after the fundamental problem. We have a better chance at that now.

PANCREATIC CANCER RESEARCH

Senator SHELBY. What about the area of pancreatic cancer? That is a fast-moving thing, I know.

Dr. COLLINS. It is, indeed. And if Dr. Sharpless is listening, maybe he would like to quickly give a response since that is his area at the Cancer Institute. Ned, are you there?

Dr. SHARPLESS. Sure. Yes. Thank you, Francis.

Pancreatic cancer is an area where we have not seen the success that we have seen in other cancers, but it is not for lack of good ideas. So, there are a number of——

One of the realizations is that pancreatic cancer comes in lots of flavors, and each one needs its own treatment. So, now we are working on the subset approach to pancreatic cancer. I think there is also a real opportunity to detect pancreatic cancer earlier at a more curable stage.

So, I think those are the exciting areas of pancreatic cancer research.

Senator SHELBY. Thank you. I would like to get in—I know my time is moving on. The chairperson has been very kind.

CTSA PROGRAM

Dr. Collins, in the area of the CTSA Program, the Clinical and Translational Science Award Program. The CTSA hubs and their partners, I think, have done a lot of good work in that area, and valuable work, especially during the COVID–19 thing. It is my understanding that the NIH, National Institutes of Health that you head, is considering significant changes to that program that would discourage hubs, like UAB, for example, in Birmingham, from forming partnerships with certain non-clinical universities in research questions.

Is this true, and why is that?

Dr. COLLINS. That is not a correct assumption. I know there are some rumors flying around about that, and there will be a public announcement about this.

Basically, just, without trying to get too far ahead of what has not been revealed publicly, I think we are trying to simplify the application process to make it easier for those hubs, and we intend to keep them going in vigorous ways; to apply when they are up for renewal in a way that does not require an application of 2,000 pages, which is what it has been. But, we would not want to do anything to discourage these collaborations that you are mentioning. Take that from me.

Senator SHELBY. Thank you. Madam Chair, thank you.

Senator MURRAY. Thank you. Senator Manchin.

Senator MANCHIN. Thank you, Madam Chairman, and thank all of our presenters. I appreciate very much them being here.

DOMESTIC DRUG SUPPLY CHAIN

My first question will go to Dr. Fauci. The Food and Drug Administration reports that nearly 40 percent of finished drugs and roughly 80 percent of active pharmaceutical ingredients are manufactured abroad. During the COVID–19 pandemic, we saw factories shut down in order to prevent the spread of virus, drug supply

chains disrupted, and drug shortages increase. As a result, America's access to essential medicines was really put into jeopardy.

As a preeminent infectious disease doctor, you know better than anyone how important it is to have access to essential medicines. So, my question will be, Doctor, can you comment on the importance of a strong domestic supply chain for essential medicines? And how can we ensure we do not experience future drug shortages when the global supply chains are disrupted?

Dr. FAUCI. Thank you very much for the question, Senator Manchin. I think it is absolutely critical that we have the capability, independent of supplies from foreign countries, to be able to supply the necessary medicines that we need in the United States. I have been of that opinion for a very long period of time.

The solution to the problem is to be doing much less of the outsourcing to foreign countries for the important ingredients of many of our medications. So, right now, we are not in that good position, and I believe, particularly since the disruptions of the supply chain that have occurred with the COVID–19 pandemic, that this might be a good lesson for us for the future to make sure we have much more dependency on what we can do domestically as opposed to in foreign nations.

Senator MANCHIN. Doctor, have you all looked at why? Why has most of the manufacturing left the United States and why are we not able to manufacture? Are we at a disadvantage in the United States for other reasons, cost wise, or basically different types of things, that we make people jump through hoops and everything else as far as permitting and all that? What would be the cause?

Dr. FAUCI. You know, Senator, to be honest with you, I do not know why that has happened. I think it was because it was felt it would be much less expensive to get this done outside, but I do not really know the answer to your question of why we have so much of a dependency of important materials outside of the Country. But, certainly, whatever the reason, I believe it needs to be corrected.

Senator MANCHIN. Well, I need to work with you on that, Doctor, if I can, basically, in making sure this Administration—I think they understand the urgency we need to start basically manufacturing again, not only just our drugs, but so many things in our Country. So, I look forward to your support on that.

RURAL HEALTH OUTCOMES

Dr. Collins, West Virginia is constantly ranked last in the Nation for health outcomes. In 2020, the America's Health Rankings reported my State of West Virginia 50th for premature deaths, frequent mental distress, and multiple chronic conditions. We also ranked last in life expectancy.

What is the NIH doing to bridge this gap in health outcomes? And how do you ensure that the medical research that you do benefits people in poor, rural communities?

Dr. COLLINS. Well, it is very troubling to see the fact that you have just cited that health outcomes are not what we would all want them to be. And, of course, there are many factors that play into that, Senator, and we are deeply engaged in research in trying to identify the ones that are addressable.

Certainly, one of the things I might point to is the increasing focus we have on disease prevention. If we simply are limiting ourselves to trying to help people who have already developed a serious disease, we have kind of missed the opportunity. Unfortunately, our healthcare system does not do a great job in that situation of providing support for disease prevention, and it seems happier to pay for things once people are already quite ill, so there is additional work that needs to be done there.

One of the things that I think I would point to is a series of large-scale efforts to really understand what are the factors that play out in people staying healthy or getting a chronic disease or how you manage that.

The All of Us Program, which this Congress has supported, on the way to enrolling a million participants, including in West Virginia, is a way in which we can collect that kind of evidence, including their electronic health records and lots of information about their environmental exposures, and try to figure out in a holistic way, how can we take that information and bring forward a better chance for people to live not just a good lifespan, but a good health span. So, we are——

Senator MANCHIN. Thank you, Doctor.

Dr. COLLINS [continuing]. Deeply engaged.

Senator MANCHIN. Thank you, sir.

Dr. Fauci, finally, you know, my home State of West Virginia is battling an epidemic during the middle of a pandemic. We have been devastated by the drug epidemic, COVID–19, and now—we now lead the Nation in new HIV infection rates. You spent much of your career focused on prevention, diagnosis, and treatment of HIV/AIDS, and your research has been instrumental in saving countless lives in the United States and around the world.

INFECTIOUS DISEASE SURVEILLANCE EFFORTS

So, Doctor, what is being done to replicate testing and surveillance efforts we saw put into place for COVID–19 for other infectious disease, like HIV/AIDS? And what public health infrastructure would be required to bring better infectious disease testing and surveillance to fruition?

Dr. FAUCI. Thank you for that question, Senator. The HIV testing situation, unfortunately, has been somewhat interrupted by the COVID–19 pandemic because of the interruption of multiple services.

But, as you know, we have a 10-year plan to end HIV as an epidemic in the United States, and that is going to require access to testing for those who are not infected to put them on, if they are at risk, to pre-exposure prophylaxis; and those who are infected to immediately put them on antiretroviral therapy. Because, as we know, when you bring the level of virus to below detectable, not only do you save the life of the individual, but you make it essentially impossible for that individual to infect someone else.

So, testing is really at the fundamental basis of how you address the epidemic and, for that reason, it is going to be extremely important to get our testing capabilities back up to snuff once we get the Country back on a degree of normality following control of the COVID–19 pandemic.

Senator MANCHIN. Thank you. Thank you, Madam Chairman.

Senator MURRAY. Thank you. Senator Braun.

Senator BRAUN. Thank you, Madam Chair.

Dr. Fauci, I was listening with interest in Senator Kennedy's line of questioning, which probably was asking you to maybe answer some things based upon what the WHO should do or not.

INVESTIGATION INTO ORIGIN OF COVID–19

I would like to discuss something that is probably a little simpler to answer in terms of transparency in general. From the time I have known you and Dr. Collins, it has generally been in this seat, and we have been talking about something related to COVID. Would you agree that in the whole process of—now that there are second thoughts on how this thing derived, that it may have come from a lab, that we should emphasize as much transparency as possible in pursuit of getting the answer?

Dr. FAUCI. Without a doubt, Senator. No doubt.

Senator BRAUN. And the next logical question would be that we do not know what we are going to get from the communist regime or the WHO, but we do know that through our Director of National Intelligence and probably DHS (Department of Homeland Security), from Haines and Mayorkas, that they have probably got information there. And, so, since you believe in transparency, wouldn't you think that we should declassify all the information that we own so that you, Americans, independent researchers, can see what we have got to sort through how this thing started?

Dr. FAUCI. Well, Senator, I have said publicly and most recently that I believe that there should be transparency, and open, fair, and independent, continue to look. As I have said, I still believe that the most likely scenario is that this was a natural occurrence, but no one knows that 100 percent for sure. And since there is a lot of concern, a lot of speculation, and since no one absolutely knows that, I believe we do need the kind of investigation where there is open transparency and all the information that is available to be made available to scrutinize.

Senator BRAUN. So, since you have been the point person on just a variety of topics through the COVID saga, does that mean then that you will ask President Biden to declassify that information?

Dr. FAUCI. I do not think I can promise you——

Senator BRAUN. But, I mean, would you ask him since you believe in transparency? Wouldn't it make sense that we get the information that we have? And I think if it does not come from you, Dr. Collins, someone that has been in the mix from the get-go, that we will not see it. And we owe it to the American people with what we have been through to at least look at the information that we have.

Dr. FAUCI. Yes. I am not sure the information we have, but—I am not sure if it is my place to tell the President of the United States to declassify——

Senator BRAUN. But you have been very engaging on a wide range——

Dr. FAUCI. Right.

Senator BRAUN [continuing]. Of topics, and I think he would respect your opinion as much as anyone.

Dr. Collins, where are you at on that subject of giving the American people the information that we house?

Dr. COLLINS. Well, I am very much where Dr. Fauci is with the desire to be as transparent as possible in this situation and really try to find out what happened. I agree with him that it is most likely that this is a virus that arose naturally, but we cannot exclude the possibility of some kind of a lab accident. That is why we have advocated very strongly that WHO needs to go back and try again after the first phase of their investigation really satisfied nobody, and this time we need a really expert-driven, no-holds-barred collection of information, which is how we are mostly really going to find out what happened.

I am just not in a position to know what might be in the classified documents and what else might be there that would not be relevant to this and might actually be harmful to national security. I get—I take your point. But, I know the President is very interested, also, in seeing truth come out here, so it may not require Tony or me to tell him that this would be good, to make this as visible as possible.

Senator BRAUN. Well, I think for the American public, if we are relying on the WHO to do it again, even though it seems like they have had somewhat of an epiphany that we need to dig deeper. I think if it does not come from the two of you to ask for simply the release of information, of course, keeping hidden anything that would be something that could not be exposed. But, I am guessing there is a good bulk of that that would be benign in terms of just the information we have about the origin of the disease.

So, I think for many of us, many Americans, with what we have gone through, we ought to at least be willing to look at the information that we have to get people satisfied that we are getting to the bottom of it. So, I would ask each one of you to think about that and see if it makes sense, have our President declassify it so we can see it.

Dr. COLLINS. Thank you.

Senator BRAUN. Thank you.

Senator MURRAY. Thank you. Senator Moran.

Senator MORAN. Chairman, thank you.

Dr. Collins—well, Doctors, welcome. Good to be here with you, and I appreciate your presence and your work.

Let me talk about clinical and translational science, if I could. Under Dr. Austin's prior leadership, the National Center for Advancing Translational Science at NIH has been essential in facilitating clinical and translational research, and I have seen it in Kansas. In fact, I have seen it with the director of that directorate.

CTSA PROGRAM

In Kansas, NCATS' Clinical and Translational Science Award Program has served for a catalyst to bring lots of organizations in the research community and community partners together to advance research.

I have concerns with potential changes that are under consideration for the CTSA Program. In particular, changes that would lower hub awards and limit CTSA partners.

Moving forward, will there continue to be consideration for ensuring that CTSA centers are located in regions in the U.S. which do not already have those hubs? There is already a limited number in the Mid-West, and I would be concerned if any new changes to the program that would make it more difficult for these hubs to compete.

And, then, I would ask the question about partners. At the University of Kansas, for example, they partner with Children's Mercy, Kansas City University of Medicine and Biosciences, Kansas State University, St. Luke's Health, University of Kansas Health System, KU Office of Research, KU School of Medicine in Wichita, and University of Missouri in Kansas City. Since the CTSA Program is focused on partnerships between regional research hubs and community partners, why would NCATS limit the ability of the program, in my view, to accomplish its goal?

Dr. COLLINS. Well, Senator, thank you for the question. I am a big fan of the CTSA Program and enjoyed my opportunity to travel to Kansas with you and see some of the things they were doing a few years ago.

And this is, I think, one of those circumstances where there seems to be some anxiety in the CTSA community about something that has not actually been announced yet, and I would like to be reassuring about this. The real intention of the change that is being proposed is to de-complicate the renewal process, which currently requires an application of about 2,000 pages that I do not think anybody enjoys putting together, and to try to make this more straightforward.

There is no intention to reduce the number of hubs. Certainly, every hub has to compete to show that they are actually using the funds wisely, and we will continue that process. And this notion that somehow the new process will discourage collaborations with other institutions I find a little hard to understand because I have no knowledge that that is at all intended to be the case, and I would personally oppose that.

Senator MORAN. Thank you for your reassurance. My question was more complicated than I wanted it to be, but your answer was very comforting.

Let me ask just a couple of specific questions.

NCATS RARE DISEASE RESEARCH

What can this committee do to support NCATS' efforts to enable and facilitate advanced important research in rare diseases for patients living particularly in rural communities?

Dr. COLLINS. Well, the NCATS is deeply engaged in rare diseases. Our former director, Chris Austin, not only was a personal promoter of that; he was the head of the international committee for rare diseases, and that tradition will continue under Acting Director, Dr. Rutter.

Certainly, the support that this committee has provided to NCATS to make it possible for that kind of investment to happen in rare diseases, for which companies probably are not going to make an investment because the market is too small, is one of the reasons that we have now made really significant progress in dozens of these rare diseases.

We are also engaged right now in a serious conversation with industry about whether there is a way, with gene therapy emerging as an even more attractive opportunity for rare diseases, to make sure that we move that forward at all due speed and not have it held up by such things as a limitation in manufacturing of viral vectors.

So, they are right in the middle of that, and the support that you all have provided has made that possible, particularly through the Cures Acceleration Network, which is part of NCATS.

ALZHEIMER'S DISEASE RESEARCH

Senator MORAN. Can one of the directors talk about the improved science this additional investment in Alzheimer's research will help fund, including a better understanding of risks and protective factors in individuals, again perhaps with a focus on rural populations?

Dr. COLLINS. That is probably me because Dr. Hodes is not here. So, yes, this committee, this Congress, has increased funding for Alzheimer's research by five-fold over the course of the last 7 or 8 years, and that has made possible all kinds of bold approaches we otherwise would not have had.

We now have dozens of new drug targets that have emerged from the very careful analysis of who gets Alzheimer's and who does not. Of course, we are all waiting to see what happens maybe next month when FDA makes a review decision about the monoclonal antibody from Biogen, Aducanumab, and that will make a big difference if they decide there is something there. But, we are not depending on that.

So, yes, I might add, this ARPA–H proposal, which is part of the President's budget, specifically calls out Alzheimer's as an area of great opportunity to do some of these very bold, aggressive, and nimble approaches that would probably not happen so easily by our standard grant mechanism.

Senator MORAN. Dr. Collins, I was confused by what I thought was all the directors were appearing, although just not all of them in person. But, thank you. You can pinch-hit for each and every one of them and you did it——

Dr. COLLINS. I will try.

Senator MORAN [continuing]. This morning. I am going to see if I can get Dr. Sharpless to come to Kansas and join us again on a visit.

Dr. COLLINS. Well, he is listening, so he heard you.

Dr. SHARPLESS. Oh, I look forward to that.

Senator MORAN. All right. Consider yourself invited, and I consider you just accepted.

[Laughter]:

Senator MURRAY. Thank you. Senator Schatz.

Senator SCHATZ. Thank you, Chair Murray and Ranking Member.

PSYCHEDELIC DRUG THERAPIES

Dr. Collins, in 2019, I wrote to you and the then-FDA commissioner requesting an update on efforts by NIH and FDA to research psychedelic drugs to treat mental health illnesses. Since then,

there have been a number of potentially promising, peer-reviewed clinical research on this topic. Can you give me an update on what the next steps may be?

Dr. COLLINS. I appreciate the question. Yes, there has been a resurgence, I think, of interest in psychedelic drugs, which for a while were sort of considered like not an area that researchers legitimately ought to go after. And I think as we have learned more about how the brain works, we have begun to realize that these are potential tools for research purposes and might be clinically beneficial.

I will just mention one, which is Psilocybin, which has now been tried in no less than three randomized, controlled trials for depression, and is showing a signal there of potential interest, and that could be quite exciting because we are looking for new approaches to that.

But, there are other trials going on with MDMA, even with Psilocybin—with LSD. I think at the moment, it is the Psilocybin that has gotten the greatest attention.

Senator SCHATZ. And what are your next steps?

Dr. COLLINS. I have been talking with the Drug Abuse Institute—and I am sorry they are not here—and the Mental Health Institute—and they are not here, so I am pinch-hitting for them, as well—about whether it is a good moment to consider having perhaps a workshop to say, okay, what have we learned so far, and what more might we want to do as far as designing the next generation of clinical trials, to see where these provide benefit going beyond depression to such things as PTSD (Post-Traumatic Stress Disorder).

So, I think over the course of the next year, we are going to want to have a hard look at this.

MARIJUANA RESEARCH

Senator SCHATZ. Thank you. In 2019, you wrote to me that the NIH is committed to advancing research on the risks and potential benefits of marijuana for therapeutic uses. In that letter, you cited a number of barriers to advancing this type of research. Are we making any progress?

Dr. COLLINS. We are making some progress. You may know that, in the past, researchers who wanted to do a clinical study on marijuana had all kinds of limitations. It took generally at least a year to get through the process of paperwork to be allowed to utilize marijuana because it is a Schedule 1 agent.

But, it was also an issue that there was only one source, which was our marijuana farm in Mississippi. When I became NIH director, I was told, hey, you are running a marijuana farm. Who knew? And that, of course, is an issue because it is a limited opportunity for access. DEA (Drug Enforcement Administration) has now given permission to expand the number of suppliers. That will help.

But, frankly, what we really need is to moderate the Schedule 1 limitation. Dr. Volkow and I have been proposing for a while something called Schedule 1–R, which would be basically a different pathway if you are going to use this material for research.

Senator SCHATZ. So, I have a bill with Senators Feinstein and Grassley, which passed the Senate, did not pass the House, to ad-

dress some of these barriers. Do I have your commitment to work with my office on this legislation?

Dr. COLLINS. I would be glad to.

NON-OPIOID ALTERNATIVES TO CHRONIC PAIN

Senator SCHATZ. Thank you. I want to talk to you finally about chronic pain and non-opioid alternatives. I passed a couple of laws in this area to enable research. And I think when people think about alternatives to opioids, they move right to—in their mind, they move right into alternative medicine. And, what I am talking about is a non-opioid, pharmaceutical solution to chronic pain, and I am wondering whether we are making progress in that space.

Because, certainly, if people find other ways to alleviate their pain—physical therapy, yoga, whatever, mindfulness—I am for all of it. But, there is still a space here for a pill that you can take to alleviate chronic pain without getting you hooked on an opioid. Where are we with this?

Dr. COLLINS. That is a critical issue, and this Congress has supported NIH in something we call the HEAL Initiative, which is—stands for Helping End Addiction Long Term. Part of that is about how to better treat people who are addicted to opioids, but a big part of it is coming up with alternatives for chronic pain management that are not addictive, that are not opioids.

As a result of that, we have partnered up with industry to basically identify promising therapeutics that attack different targets in the pain mechanism that might, therefore, be beneficial. Such things as a sodium channel, for instance, called Nav1.7, that is involved in the pain transmission. But, if you block that, it should not give you any risk of addiction. We are making real progress there.

We have something called EPPIC-Net, which is bringing onboard promising compounds, getting them into Phase 2 trials as part of the HEAL Initiative. I could give you a lot more information about that if you would like.

Senator SCHATZ. Thank you. And I will just submit this one that you can consider for the record.

The U.S. has the same Federal trust responsibility for native Hawaiians as it applies to Alaska natives and American Indians, and I am hoping that you will consider expanding the scope of the Tribal Health Research Office to include native Hawaiians. I will get you a more full question for the record and look forward to your response. Thank you.

Dr. COLLINS. Glad to look at that.

Senator MURRAY. Thank you. Senator Hyde-Smith.

Senator HYDE-SMITH. Thank you, Madam Chairman. Thank you for holding the hearing, and thanks to all the witnesses who are participating today, and I certainly appreciate your willingness to serve. That is not lost here, for sure, with the past year that we have had.

FIREARMS RESEARCH AND FIREARM REGISTRIES

Dr. Collins, I wrote to you last November to express my concerns that projects recently funded by NIH disregard the spirit, long-established policies against creation of a Federal firearms registry.

And particularly, an NIH grant to Northwell Health of New York provided Federal funds for the hospital to ask the questions about lawful gun ownership of every patient seeking healthcare for any reason whatsoever at the hospital's emergency department.

Even more concerning, every member of the advisory committee overseeing the grant has been a very outspoken advocate for expansive gun control, including bans on large classes of common and popular firearms.

I have long been concerned about how firearm registries can undermine the ability of law-abiding citizens to exercise their Second Amendment rights. Several provisions of Federal law already prohibit data collection related to lawful gun ownership, and I have introduced legislation to strengthen these provisions even further.

Dr. Collins, given that President Biden is seeking increased funding for grants like the one awarded to Northwell, how are you making sure that such projects do not infringe on Americans' constitutional gun rights or violate Federal statutory prohibitions on gun registries as they stand right now?

Dr. COLLINS. Senator, I recall your letter, and we looked closely at that particular grant from Northwell and what they were proposing to do.

First of all, I think we can all agree that gun violence, which takes about 40,000 lives every year, is something that does deserve close attention and scrutiny as far as the research that we might be able to do to understand what are the causes and how to save those lives if it is possible to do so. So, we will actually be glad to pursue those opportunities.

But, we are mindful of the prohibition that Congress has put forward many years ago about not advocating for gun control, and we have been pretty careful about that. I think in that instance, the particular grant, while you are right that they were asking for this information, it fell somewhat short of what most people would have called a broad concept of a gun registry. And I think that is, if I remember, what we said in the letter in response to you.

But, I want to promise you, we are going to be very sensitive to those issues, as we now, with the President's budget, seek to see if we can do more to try to identify reasons that gun violence is so prominent and what research might teach us about how to save lives.

Senator HYDE-SMITH. Thank you. I appreciate your consciousness of that.

ORIGIN OF COVID–19

And this question may have been asked before. I have been in another hearing. I hope I am not being redundant. But, like many of my colleagues, I firmly believe we need to get to the bottom of the origin of COVID–19, and this seems even more important after this week's Wall Street Journal report that three researchers from China's Wuhan Institute of Virology sought hospital care in November 2019—for symptoms consistent with COVID–19.

First, I want to go down the line for all of our witnesses of how strongly do you believe that it is possible that the origin of the COVID–19 pandemic resulted from a leak of the virus from the Chinese lab?

And second, Dr. Fauci, I would like to ask you specifically, how is your institute working to get to the bottom of the origins of COVID–19, including exploring the laboratory leak theory?

So, I am going to start with the entire panel for the first question of, how strongly do you believe that this is possible?

Dr. COLLINS. Well, I will start, and then others can respond. Again, I will say, I think the most likely reason, mechanism, by which SARS-CoV–2 arose was a natural process of transfer from an animal to humans, but it is certainly possible that other options might have occurred, including a possible lab leak. We just do not have evidence to be able to say what that likelihood is.

Dr. Bianchi.

Dr. BIANCHI. Yes. So, I would agree with Dr. Collins. We have no personal knowledge of anything that might have happened in China at the National Institute of Child Health and Human Development, but we fully support a full investigation of getting at the facts.

Dr. COLLINS. Dr. Gibbons. Dr. Gibbons, are you there?

Dr. GIBBONS. Yes. I concur with my colleagues in terms of transparency is a critical part of this.

Dr. COLLINS. Dr. Sharpless, I think I saw you on the screen.

Dr. SHARPLESS. Sure. Yes, Senator Hyde-Smith, I saw the same report and I found that concerning. I think lab accidents happen and we need to investigate the possibility. Although I think many of us feel zoonotic transfer is perhaps more likely, I think we should investigate all possible explanations.

Dr. COLLINS. Dr. Pérez-Stable.

Dr. PÉREZ-STABLE. I concur with my colleagues. I think of concern, but certainly we need evidence.

Dr. COLLINS. And Dr. Tromberg.

Dr. TROMBERG. Yes, I agree with my colleagues, as well, and would like to see more investigation.

Dr. COLLINS. Dr. Fauci.

Dr. FAUCI. Yes. As I have said many times, I feel the likelihood is still high that this is a natural occurrence. But, since we cannot know 100 percent whether it is or is not, other possibilities exist and, for that reason, I and my colleagues have been saying that we are very much in favor of a further investigation to the next phase from the WHO, who has already done a phase one. And, we are strongly in support of continuing that to a phase two investigation.

Senator HYDE-SMITH. Thank you——

Senator MURRAY. Thank you.

Senator HYDE-SMITH [continuing]. Very much, and I yield my time.

Senator MURRAY. Thank you so much. Senator Baldwin.

Senator BALDWIN. Thank you, Madam Chair.

Last week, I had the privilege of joining some of my colleagues on a visit to the National Institutes of Health. While much of our discussion was centered on the response to the COVID–19 pandemic, I was struck by the broad applications of the innovation that we have seen during this time.

ADVANCES IN VACCINE AND THERAPEUTIC DELIVERY SYSTEMS
(RADX PROGRAM)

And, I have often spoken about the Wisconsin-based company, FluGen, which is working to make vaccines that can be administered as a nasal spray. I also believe that this type of innovation is key in terms of how we think about our ability to respond to future pandemics.

Dr. Tromberg, it was great to see you on that trip to NIH. I wonder if you could describe how engineering advancements have contributed to our response to COVID–19. And, how are you thinking about the future of delivery and administration of vaccines and therapeutics? And, how will these advancements help us prepare for the future?

Dr. TROMBERG. Thank you, Senator Baldwin, for the question, and it was great to meet you last week, or I guess it was 2 weeks ago when you came to visit.

So, for COVID, we have supported a wide range of technologic advances in medical imaging and artificial intelligence, digital health platforms, PPE (Personal Protective Equipment), ventilators, new therapeutic approaches. Of course, the biggest probably and most impactful has been the RADx testing program, which has delivered, as you have seen, more than 300 million tests, including over-the-counter tests with very advanced technologies from nanoscience.

In terms of vaccines, this is a very exciting area. Another one that we have had in our portfolio, one of the strategies that we have been supporting, are micro needle patches. So, imagine a dime-sized micro needle patch that has got—the needles are entirely soluble in water, and as soon as you put them into your skin, they start to deliver the vaccine. After the delivery, the needles are all gone, and you throw the patch away. You get a new one in the mail. So, this has moved into Phase 1 clinical trials. Efficacy has been shown.

I might, if you have a moment, toss it over to Dr. Fauci because we have collaborated with his institute in the development of these new delivery approaches and they may have some other approaches, as well.

Senator BALDWIN. Please. Dr. Fauci.

Dr. FAUCI. Thank you, Bruce. Yes. We have an active collaboration with Dr. Tromberg's Institute and we are looking towards the future about how we can make it much easier to get people vaccinated. This is of particular relevance right now because, with COVID–19, even though we are doing really very well with vaccination, we still have a group of individuals who were really difficult to get to. And hopefully, when we have a much easier way to administer the way Dr. Tromberg has mentioned, that will make it easier for us.

Senator BALDWIN. Excellent. In April, the University of Wisconsin launched the Center for Health Disparities Research Center, which has a leadership team comprised entirely of women, will focus on how physical environment and social conditions intersect to influence an individual's health.

Their first initiative, funded by the NIH, will use data from 22 Alzheimer's disease research centers throughout the U.S. to examine how social determinants of health throughout a person's lifetime impact their brain health.

The pandemic has made it clear that we need to do more research like this to better understand and respond to health inequities, and I applaud the work of Dr. Amy Kind and the University of Wisconsin. It is imperative that we maintain our commitment to this into the future.

COVID–19 AND HEALTH DISPARITIES

So, Dr. Pérez-Stable, how has the impact of the COVID–19 pandemic on communities of color informed how NIH thinks about studying health disparities going forward? And what additional investments are needed to fill these gaps?

Dr. PÉREZ-STABLE. Thank you, Senator Baldwin, for that question. I think a year ago, when we understood the dimension of the dramatic, disproportionate burden by race, ethnicity, and socioeconomic status on the population, there was sort of an aha moment for all of NIH to say, this problem has been with us for a long time. We have made limited progress. It is time we put our innovation, our efforts, to address this.

Out of this effort, we created the Community Engagement Alliance Against COVID–19. Dr. Gibbons and I are co-chairing that. Dr. Collins mentioned it in his opening statement. And I think to heighten the importance of community engagement, so talk to the people that are affected, bring them in as full partners, identify the problems, and then mobilize all sectors that we can mobilize. Not just the researchers and the healthcare clinicians, but also the housing, transportation, zoning, all the different sectors of society, to see how we can begin to make a difference in this setting.

And I applaud the effort of Dr. Kind. She was a grantee of ours, as well as others, and also applaud the effort of looking at existing data with standardized measures to address problems of this kind, like Alzheimer's disease.

Senator BALDWIN. Yes. Thank you so much.

Madam Chair, I yield back.

Senator MURRAY. Thank you. Senator Rubio.

Senator RUBIO. Thanks, all of you, for being here.

I think I will direct this to Dr. Fauci, but I welcome everybody's answer. I just want to go through, so, what we do know. We have heard a lot about what we do not know.

So, here are the things that we do know, okay?

ORIGIN OF COVID–19

So, SARS–1, we identified the host animal within 4 months.

MERS, I believe, we identified the host animal within 9 months.

It has now been 15 and a half, 16 months, we have still not seen and China has not produced any evidence of the host animal that transmitted COVID–19 to a human.

We know that China has a history of lab accidents. I think, Dr. Fauci, you answered Senator Graham's question. I think he phrased it as, has there ever been a pandemic that came out of a laboratory, and the answer was no.

But, we know of outbreaks that came out of a laboratory. I believe back in 2004, two researchers in Beijing were infected doing research on SARS and it led to an outbreak. China has a history of lab accidents.

This outbreak happened in a city that happened to be the home, coincidentally, of a lab which we know is involved in extensive research. And, what they do is they take this naturally-occurring virus and they manipulate it and they change it to make it infectious to humans. We know that they do that there. They have published about it.

And, it also happened in a city in a lab where a Rutgers biosecurity expert raised concerns about its safety, and our diplomats in 2018 were cabling back to Washington expressing concern about the safety.

So, I take all those facts together, right?

SARS, we knew the host in 4 months.

MERS we knew the host in 9.

We still do not know the host in—for COVID, even though—and China is not being transparent about it even though they have a vested interest in producing the host so they can put all this down.

In a lab that we know is involved in changing viruses synthetically so that they become infectious for humans.

In a lab that diplomats have told us is unsafe.

In a country that had history of lab leaks.

And, by the way, in a virus that we know can be synthetically-created because the Swiss did it. The Swiss created an exact replica of this virus in the lab for purposes of answering it.

All of these facts were available to us last May, last April. Why—I will start with Dr. Fauci. Why did you dismiss the lab leak theory as credible?

Dr. FAUCI. I have always said that the high likelihood is that this is a natural occurrence. I did not dismiss anything. I just said it is a high likelihood that this is a natural occurrence from the environment of an animal reservoir that we have not yet identified, and I still maintain that.

But, as I just mentioned in response to other questions, that since you do not know 100 percent about that, because no one knows, including me, 100 percent what the origin is, is the reason why we are in favor of further investigation.

Senator RUBIO. Well, given everything I have just cited—and if anything I just cited is incorrect, I hope I will be corrected. I am relying—obviously, not my field of study, so I am relying on what other experts have published. What is the basis for this high likely—what is the basis for the conclusion that it is likelier to have been naturally occurring than a lab accident?

I asked a specific question to the Director of National Intelligence, and how I posed it is, is it not true that it is the assessment that they are equally likely, based on our information that we have.

So, as I outline all of these things here, is she wrong when she answered me yes? And, based on everything I have just cited, why the—what is it that we are basing the higher likelihood of naturally occurring? Is it simply because that is all we have ever seen in the past?

Dr. FAUCI. Well, we have historical experience that happened with SARS–CoV–1. It happened with MERS. It happened with HIV. It happened with virtually all the influenza pandemics. So, the historical basis for pandemics evolving naturally from an animal reservoir is extremely strong, and it is for that reason that we felt that something similar like this has a much higher likelihood.

But, again, getting back to what I said—and let me repeat so there is no lack of clarity in that. No one knows, not even I, 100 percent at this point, which is the reason why we are in favor of further investigation.

Senator RUBIO. But, going back to precedent, precedents require them to be similar. The difference between this one and that one is—as I said, 4 months we knew the host for SARS, at 9 months we knew the host for MERS. China has all the incentive in the world to produce this host and has not done so. And, then, you add up all these other things, I mean, is it just a coincidence it happened in the city that is doing this kind of research, which, by the way, is controversial? I know you and others have been supportive of it, but it is controversial. It is not widely accepted as good.

My whole point is there are people out there who had Facebook posts taken down. They are called kooks, conspiracy theorists, for saying publically a year ago what we now say may be possible. I think those people deserve an apology, at a minimum.

Thank you.

Senator MURRAY. Thank you.

COVID–19 AND MIS–C

Dr. Bianchi, thank you. NICHD (National Institute of Child Health and Human Development) is trying to develop ways to identify children at high risk for multi-system inflammatory syndrome in children. It is a rare and life-threatening after effect of COVID–19. Now, while most children who become infected, I know, have mild or no symptoms, some do go on to develop this severe and sometimes fatal condition. I know your research is still in the early stages, but could you describe the NICHD's efforts to develop clinical, predictive models using machine learning to identify children at risk and how physicians are using this testing device and data?

Dr. BIANCHI. Thank you very much for your question, Senator Murray. As you know, there are almost four million children who have been infected with SARS–CoV–2, but the key is to figure out which is the one-in-a-thousand child who is going to get very sick with this MIS–C, and that child could get critically ill, although most do recover. So, as a parent, you would want to know if my child tests positive, what is going to happen.

And, so, as part of the RADx RAD program—NIH is supporting this. It is four different programs CARING for Children with COVID, but the predictive one that is using artificial intelligence and machine learning is called the PreVAIL Kids Program. And what that is, is it is eight different programs around the Country, with some international partners, that are using existing cohorts, as well as prospectively enrolled cohorts, to collect biospecimens and use artificial intelligence in conjunction with the electronic health records.

The program started within the past few months, so we do not have evidence yet. But, the enrollments are on target, and we are expecting to enroll about 12,000—actually, we have already enrolled about 12,000 children out of 16,000 that are expected.

A.I. DETECTION OF CANCERS

Senator MURRAY. Okay. And Dr. Sharpless, artificial intelligence has been shown to help improve the detection of breast cancer in mammograms, and lung cancer in CT scans. And suggesting that AI appears well suited for imaging, are you looking at the potential for AI to help early detection of other cancers?

Dr. SHARPLESS. Oh, yes. This is a very important topic. I think artificial intelligence has really the ability to transform cancer research and cancer clinical care in dramatic ways.

We have a very lively set of collaborations going on with the Department of Energy that has extensive expertise in this topic. To use, you know, AI to try and identify drug targets for medicinal chemistry, or to use AI to read 600,000 pathology reports that we get for the SEER database every year, or to use artificial intelligence for image analysis, both pathology images and radiology images.

So, I think this is a tremendously exciting technology that has real opportunities to advance cancer research and cancer care in many important ways.

I think we were also worried about the ethical issues of AI, and we want to make sure that we use practices that will not reinforce biases that are latent in some of our data sets.

But, overall, I think the promise of AI is very exciting for cancer research.

Senator MURRAY. Interesting. Okay.

CLIMATE CHANGE AND HEALTH

Dr. Gibbons, the request, budget request, includes $110 million to study the impact climate change is having on health. Talk to us about what kind of serious effects have we been seeing from climate change, and what kinds of research do you expect NHLBI (National Heart, Lung, and Blood Institute) to support with this kind of funding?

Dr. GIBBONS. Yes. Thank you for that question. As we know, climate change often involves these changes in our air, in our air quality, particularly it is likely to promote more air pollution. Certainly, the constituents on the West Coast are familiar with the impact of wild fires on air quality.

And although air is all around us, air pollution tends to concentrate and have its greatest impact on certain communities, particularly communities in which those neighborhoods are closer to sources of air pollution, and therefore, the impact is also inequitable in terms of the health consequences of air pollution, and that is falling on the most vulnerable.

We know that it exacerbates certain chronic conditions, certainly cardiopulmonary ones like chronic obstructive pulmonary disease, asthma, heart failure. Heart attacks are increased in the context of higher air pollution promoted by climate change.

And, we anticipate that there will be a need to not only mitigate the impact of climate change, but also to enhance resilience to the effects of air pollution on health, and we anticipate that that will involve enhancing healthy communities that are disproportionately affected by the consequences of air pollution derived from climate change. And our programs that are community-engaged research with that health equity lens should be promising in that regard.

Senator MURRAY. Okay. I think this is really important, and I think we all should recognize that this is an area we need to look at, so I appreciate your work on this and we will be following it closely.

I will turn to——

SEXUAL HARASSMENT AT NIH

Okay. I have one additional question and that is for Dr. Collins. In 2018, the National Academies, as you know, released a report that found that nearly 60 percent of women in academia have experienced—60 percent—have experienced sexual harassment on the job and recommended that Federal research agencies require institutions to notify them when individuals on grants have violated harassment policies or put on administrative leave due to harassment allegation. And other science agencies, like National Science Foundation, have implemented these changes.

Tell me, what is NIH doing to require its research institutes to do the same?

Dr. COLLINS. Senator, I share the sense that this is an extremely important issue. The National Academy report that you mentioned I think really got everybody to recognize how pervasive sexual harassment is and what a significant negative it has been for far too long for women in our scientific workforce.

We conducted our own working group in the Advisory Committee to the Director that reported to me in December of 2019 and made a series of very significant recommendations about how we might change our approach to this. We have been working through those and have already implemented a significant fraction of them. There are some that still require some additional legal authority that is hard for us to be able to do at the present time.

In terms of what you are particularly pointing to, we have had now more than 300 allegations that have been brought to us about sexual harassment in our grantee institutions; others within our own intramural program. Of those 300, about 30 percent of them have turned out to be actually entirely validated. That has resulted in a hundred different changes in grants that—particularly, removal of principal investigators and replacement of those with other individuals.

One hundred and twenty-five individuals have been taken out of our pool of peer reviewers because of this kind of concern about the bias that they bring to that experience.

And we have made it very clear to our institutions that we expect them to report any circumstance——

Senator MURRAY. Well, expecting them does not require them to.

Dr. COLLINS. And, Senator, you and I are in an interesting discussion here that I agree—I wish we were able to simply say require. At the present time, legally, we are told we do not have that

authority. We would have to go through a 2-year rulemaking effort, or we would need statutory assistance.

Senator MURRAY. Well, okay. This is really important, and whatever we need to do, I do not—you know, I know you have worked on it, I know you have focused on it, but I know of women who have left our scientific research institutes because of this. We cannot afford to have that happen for a thousand reasons. So, whatever it is we need to do here, we need to know what it is so we can do it.

Dr. COLLINS. I am so with you. And if there is another iteration we can take at this to try to figure out—I will say that what we have said in terms of the expecting response from our institutions has gotten their attention in a pretty remarkable way. Even without requiring it, we are seeing reporting coming through.

Senator MURRAY. Well, to every one of them that is listening, I am not done with this.

Dr. COLLINS. Okay.

Senator MURRAY. Senator Blunt.

Senator BLUNT. Thank you, Chair.

I have three or four questions. Let me eliminate a couple of other topics by just making a couple of comments on some things that have already been said, one, and one thing that has not been, I do not believe, brought up today.

One is on the CTSA awards. None of the people talking to us that are current recipients think that this simplifying the process makes it more likely that they will get the research bench-to-bedside result that they think you want and they think is the key to this award.

And, you have heard a number of schools mentioned, and University of Washington would be one of them that Senator Murray would be very familiar with. Washington University in St. Louis collaborates through this program with Saint Louis University and the University of Missouri to get to more rural hospital settings and do things. So, I suspect you have heard a number of concerns about that today.

I have not heard brought up one of my concerns, which I am just going to mention. I do not think you need to respond to it. I do think that waiving the intellectual property rights on COVID–19 vaccines is a problem. I think it is a problem because I do not think it actually would increase the number of vaccines, the capacity to produce a vaccine that has efficacy, in the timeframe we need to make it. It probably is not benefitted much by waiving the rights to the research. The WTO (World Trade Organization) has to unanimously agree, which I do not think they do. But, if they do, we give our research to everybody.

And third, when this comes up again, companies would have less willingness, I think, to step forward. At least one of the companies, Dr. Collins that we dealt with in Warp Speed, there was no agreement at all that if they were not successful—we had a contract. We would buy 100,000 doses, but only if they were FDA authorized. So, they were out there totally on their own, as these companies you would expect to be.

I do not think this is likely to happen because of the WTO, but I have some concerns that I suspect are shared by others at NIH.

IMPACT OF COVID–19 PANDEMIC ON CHILDHOOD DEVELOPMENT

Dr. Bianchi, just the title—let's just take the title of your Institute and look at COVID. What do you think the impact on child health and development of COVID and the COVID environment, the pandemic environment, the quarantine environment, has been? And how are we going to be looking at what the long-term ramifications of that might be and what advice we may be able to give to schools and moms and dads and behavioral health and other health providers as it relates to child development impacted by this?

Dr. BIANCHI. Thank you so much for that question, Senator Blunt, because children, you know, have not—I think they are so important in terms of our Nation's future, first of all. But, the fact that children have been home from school has affected the entire family, has affected the workforce, et cetera.

But, because children in general have been asymptomatic or mildly symptomatic, they have not gotten as much attention, and yet being at home, being away from in-person schooling, I think may have significant impact for years to come. And, for that reason, we are trying to get the kids back to school as soon as possible.

And as part of the RADx Underserved Population program, we are also leading an initiative to really develop, evaluate, and implement testing, along with mitigation, of, you know, hand washing, social distancing, et cetera, to get evidence to reassure people to get kids back to school. Two of the sites are actually in Missouri, and one is in Washington State. There is a program in Yakima, and there is a special program in Missouri that is looking at how you deal with kids who have intellectual disabilities and cannot mitigate in the same way.

So, to answer your question, I think there will be long-term effects. I think the answer is to get kids back to school safely, with evidence. And, this program is based on a funded project that was very successful in North Carolina that showed with all the mitigation, with the work with the superintendents of schools, that the secondary infection rate in schools was extremely low compared to the community.

Senator BLUNT. Yes. I would think here that some of the developmental issues, and they will be different with 4 and 5 year olds and kindergarten and first grade than they will people in seventh grade, and those may be different than people——

Dr. BIANCHI. Absolutely.

Senator BLUNT [continuing]. In the eleventh and twelfth grade and how—you know, I think we are going to have to watch this carefully and try to get data and then share that data.

FUTURE OF MRNA TECHNOLOGY

On vaccines—actually, on—maybe more on mRNA than vaccines, what do we think the impact may be as it relates to cancer, to HIV? We will start, Dr. Fauci, with you. Can we look at the flu shot in a different way? And what do we think the mRNA impact, now that we know this different use for it, may have on other healthcare settings? And Dr. Sharpless, I am going to come to you second on this.

Dr. FAUCI. It is going to—I believe, and many of my colleagues believe, that the mRNA technology, as it has been so spectacularly successful with SARS–CoV–2 to develop a vaccine against COVID–19, is already being pursued for other infections, including HIV and including influenza. So, there are a couple of things that are going on now. Even as we see the successes with COVID–19 in using the mRNA technology for the development, for example, of universal flu vaccines, as well as now having HIV vaccine researchers now looking at the possibility of an mRNA platform technology to use for HIV. So, it is already happening.

Senator BLUNT. Dr. Sharpless, on mRNA, I mean, we know the impact in just the last half dozen years of immunotherapy on cancer treatment. What about this mRNA intervention and how it might impact the way we look at fighting cancer?

Dr. SHARPLESS. Yes, this is a very exciting topic. You know, people interested in this space have been working on this, you know, long before the pandemic. So, using mRNA for cancer therapy has many potential applications because you can really get the body to make a protein, and that protein could have a desirable effect against cancer, for cancer therapy, in a lot of ways.

The furthest advance, as you mentioned, is the use of mRNA vaccines, you know, cancer vaccines. And clearly, they tend to be highly personalized, the ideas that you can sequence someone's own tumor and then make the vaccine to their very own tumor in a way that will not cause them autoimmune side effects, and this is an idea to augment other kinds of autoimmune cancer—or anti-immune cancer therapies.

So, it is a very promising area. It is in clinical trials, and we just need to see how this develops.

Senator BLUNT. Thank you. My last question, Chair.

IMPACT OF COVID–19 PANDEMIC ON RESEARCH AND RESEARCHERS

Dr. Collins, in the pandemic, particularly with lab closings, we obviously lost some time, and lost research that is going to take a long time to recreate. Are the lab reopenings happening in the way they need to? And, do you have the flexibility to extend a grant to overcome the disruption? And probably just not this disruption of the time closed, but the research lost by closing, as well.

Dr. COLLINS. I am glad you are asking because this is yet another of the terrible casualties of this terrible pandemic. It has been very hard on researchers, especially those who need a laboratory to do their work or who were running a clinical trial that was very hard to enroll participants. And, yes, we did have to have many of those folks staying away from the workplace for their own safety.

They are coming back. Our own program at NIH, our intramural program, now is up to about 50 percent occupancy, but it is not anywhere near where it was pre-pandemic. We have done everything we can with our flexibilities to try to make sure, particularly, that trainees and early-stage investigators do not get further injured by this by extending the periods of their training; or by allowing grants if they are able to put forward a special request to be extended for an extra year, either without extra funds, or with, if the case is strong.

And yes, I also think we need to be cognizant of the way in which this is affecting people in other ways. We have now come up with a way to provide childcare support for our trainees who otherwise have not had that, and that has been one additional burden on their shoulders.

Our estimates are that it is about a $16 billion loss that has occurred because of the way in which this has affected research in our extramural institutions; that they are in a tough place to try to make up. So, I appreciate your asking the question.

We are going to have a really big challenge getting ourselves back into the place that we were before this happened.

Senator BLUNT. Well, let us know what we need to be thinking about as we think about the rest of this bill on that topic. And thank you, Chair.

Senator MURRAY. Thank you very much. And I want to thank all of our witnesses today for their really—for a really productive hearing. I think we all learned a lot. So, thank you very much.

ADDITIONAL COMMITTEE QUESTIONS

For any Senators who wish to ask additional questions, questions for the record will be due one week after the President's budget is delivered at 5 p.m. The hearing record will also remain open until then for members who wish to submit additional materials for the record.

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

QUESTIONS SUBMITTED TO DR. FRANCIS COLLINS

QUESTIONS SUBMITTED BY SENATOR PATTY MURRAY

Question. The President's fiscal year 2022 skinny budget proposed a major new biomedical research effort by establishing ARPA–H. While the skinny budget was light on details regarding the structure of the program, the Administration's statement indicated that the initial focus of ARPA–H would be 'on cancer and other diseases such as diabetes and Alzheimer's.'

Assuming Congress and the Administration work together to establish ARPA–H, how would you envision ARPA–H setting priorities for research into additional diseases?

Answer. Over the long term, the proposed structure for the Advanced Research Projects Agency for Health (ARPA–H) is intended to empower the ARPA–H leadership and staff to set and execute on research priorities for a variety of high-risk, high-reward, milestone-driven projects that can lead to novel capabilities, platforms, and resources that are applicable to a range of diseases.

For the initial direction, the Administration is working to set up multiple pathways, both within the government and the broader stakeholder community, for priority setting and for exploring new areas ripe for research at ARPA–H. At the time of this hearing, the White House Office of Science and Technology Policy (OSTP) and the National Institutes of Health (NIH) are in the planning phases of convening multiple listening sessions with key stakeholder groups including patient organizations, industry, venture capitalists and philanthropists, and others from the academic and research communities. During these sessions, stakeholders will be asked to offer their perspective on what they see as the greatest research challenges and opportunities that could be addressed using the ARPA–H model. This input will help refine the scope and provide a wealth of ideas for the first ARPA–H director to consider as they develop the agency's vision.

In mid-July, the Administration established a Joint Fast Track Action Committee (FTAC) to help steer the creation of ARPA–H and lay the groundwork for strong interagency coordination. OSTP and NIH serve as co-chairs of this committee that includes representatives from Department of Agriculture, DARPA, Office of the

Under Secretary of Defense for Research & Engineering, ARPA–E, BARDA, CDC, CMS, FDA, VA, EPA, NSF, and the Smithsonian Institution, among others.

Question. Some of the greatest advances in medical innovation in the last decade have been brought on through genetic analyses and use of sophisticated computer programs that can shorten the time taking drug candidates through clinical studies. In fact, the development of COVID–19 vaccines benefited from the use of 21st century technology like cloud computing and AI to help stop the virus' spread and save lives.

How will the President's budget build on the use of modern tools like cloud computing, AI, and genetic analyses to further accelerate the delivery of cures to patients?

Answer. Over the last decade, pharmacogenetics has advanced the frontier of personalized medicine such that drug therapeutics are developed based on the genetic aberrations of disease. This approach is most notably applied for cancer treatments and also other diseases. Cancers of various types are treated by first knowing the genetic mutations and/or deletion of genes. Then drug candidates are screened and developed by computer modeling of the target sites along with potential drug candidates. Such modeling requires various large datasets and analytics that, if stored in the cloud and interoperable, can be mined to find the best drug candidates that bind to the target sites for treatment. Storing large datasets in the cloud is only the first requirement for cloud computing. Such computation requires new tools, and support for tool development is essential to realize the opportunities for cloud computing.

Artificial intelligence (AI) has advanced the pace of drug discovery and development via predictive models of drug/target interactions and also facilitates clinical trial design based on algorithms for go/no go decisions during the trials.

The President's Budget Request supports the application of AI to improve diagnostics for diseases as diverse as coronavirus disease 2019 (COVID–19) and cancer. In each case, information-rich data sources that are stored, aggregated together, and analyzed in the cloud are used to rapidly train and test these new capabilities. New programs like the Artificial Intelligence/Machine Learning Consortium to Advance Health Equity and Researcher Diversity program, or AIM–AHEAD, and Bridge2AI will harness AI for health by generating AI-ready datasets and best practices for machine learning. This will allow researchers to accelerate data-driven discovery for grand challenges in biomedicine using AI-based technologies. Additionally, NIH's partnership with cloud services providers—Google, AWS and now Microsoft Azure—further enhances researchers' abilities to leverage industry technologies and utilize AI-ready data for drug discoveries and therapeutic treatments.

QUESTIONS SUBMITTED BY SENATOR RICHARD J. DURBIN

Question. I have worked with the Subcommittee Chair and Ranking Member for years on sustained, predictable increases to the NIH budget—with the goal of providing at least 5 percent real growth year-over-year. We have had success, leading to a 42 percent increase over the past 6 years, along with supplemental funding in COVID–19 relief packages. The President's fiscal year 22 budget calls for a 19 percent increase to the NIH overall budget. The vast majority of that comes from the proposed creation of a new advanced research effort, called ARPA–H. When I toured the NIH campus recently with many members of this Subcommittee, you discussed how innovative efforts during the pandemic—such as with the RADx testing program or Warp Speed vaccine development—align with the ARPA-H proposal, incorporation closer partnerships with industry and coordination at different stages in the research and development of promising breakthroughs. Your testimony discusses application of this nimble ARPA–H proposal for cancer, infectious diseases, and autoimmune diseases.

As we evaluate this proposal, what are the core aspects of this ARPA–H policy that you want us to keep in mind?

Answer. We envision that the Advanced Research Projects Agency for Health (ARPA–H) will be able to tackle large-scale challenges using a proven high-risk, high-reward approach that embraces nimbleness and flexibility with the broader goal of delivering rapid breakthroughs that serve all patients. Being successful in this endeavor requires close communication and collaboration across government and with key stakeholders in the external biomedical community. This could include undertaking projects with Federal agencies, private companies, independent research institutes, medical centers, as well as academic institutions—all collaborating to advance innovative health research. NIH deployed similar approaches in response to the COVID–19 pandemic (Accelerating COVID–19 Therapeutic Interventions and

Vaccines, or ACTIV and Rapid Acceleration of Diagnostics, or RADx)—which yielded life-saving results for Americans, and also served as a learning opportunity to appreciate further the value of employing a DARPA—like model to support research. With Congressional support, we believe we can leverage these models in other areas of health research to drive transformative change and impact.

Question. We have spoken in the past about two seemingly divergent issues. On one hand, we talk about the need to invest in medical research to find breakthroughs and cures for patients, so we rightfully appropriate billions into NIH-funded research—sign me up for that. But then these drugs come to market—the vast majority of them benefitting from NIH research (e.g. a study finding that all 210 drugs approved by FDA between 2010 and 2016 benefitted from NIH-funded research in some form)—and too many of them with exorbitant price tags. Recent studies show that high costs contribute to poor medication adherence, including with one-quarter of cancer patients choosing not to fill a prescription due to cost. I know Dr. Sharpless has talked about the "financial toxicity" for cancer patients. Americans pay the highest prices for medications in the world, with a recent GAO report finding that the U.S. pays two- to four-times more for certain medications than other developed countries. It is counterintuitive and an outrage that taxpayers fund cutting-edge research, which leads to drugs, that we often cannot afford once they hit the market. I understand NIH does not set drug prices and does not want to limit the handoff or development of its research to stakeholders that commercialize the discoveries. But the current system does not maximize the benefits for patients.

Given the role of NIH research in contributing to FDA-approved medications, many of which come with extremely high price tags, what specific steps can NIH take to ensure that patients are able to afford the incredible discoveries made at NIH?

The NIH has received several petitions to exercise march-in rights (35 U.S.C. § 203), but has never done so.

—Under what circumstances would NIH consider doing so?

—Under that statutory authority, how does NIH define and evaluate the term "practical application" for the purposes of how a contractor or assignee makes a subject invention funded by NIH available to the public on reasonable terms?

—What are the factors used in such definition and evaluation?

—Can you provide an example of the analysis undertaken in evaluation of a previously filed march-in-petition?

Answer. The National Institutes of Health (NIH) shares your concern about the high price of drugs and the impact on public health. The article you reference shows that all of the 210 drugs approved by U.S. Food and Drug Administration from 2010 to 2016 were based on at least one scientific publication reporting on research funded by the NIH.[1] The researchers reported that 96 percent of the NIH funded projects were identified based on a search for the "target" rather than the drug itself. Identifying a drug target, meaning a protein in a cell that has a function in a disease process, opens the door for any researcher in industry or academia to screen for drugs that bind to the target to slow or arrest disease processes. This research is key to a vibrant drug discovery process in the United States and does not limit discovery to one drug for each target. The development of multiple drugs for a particular disease allows the patient and physician to choose the best one for them and can lead to price competition in the market. Drug pricing is a complex problem that involves various segments of the market, much of which NIH has no control over. A smaller number of important drugs utilize patented inventions funded by the NIH. When NIH has been asked to consider march-in under the Bayh-Dole Act based on the price of such drugs, NIH has stated that the issue of drug pricing is one that should be address by Congress, as it considers these matters in a larger context.[2]

The Bayh-Dole march-in provision (See 35 U.S.C. 203) allows a government funding agency to require a grantee to grant a license to a patent of an invention made under that agency's awarded grants or contracts and allows other "responsible applicants" to obtain the license if one of four circumstances are met:

1. the contractor or assignee has not taken, or is not expected to take within a reasonable time, effective steps to achieve practical application of the subject invention in such field of use

2. to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees

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[1] Cleary et al., 2018, www.ncbi.nlm.nih.gov/pmc/articles/PMC5878010/.

[2] NIH march-in responses from 1997–2013 at ott.nih.gov/policy/policies-reports under "NIH March-In Response".

3. to meet requirements for public use specified by Federal regulations and such requirements are not reasonably satisfied by the contractor, assignee, or licensees

4. the agreement required by section 204 [a requirement that patented products be manufactured substantially in the United States unless a waiver is granted]

The first two criteria are typically cited in petitions to consider a march-in by the National Institutes of Health (NIH). For example, if a company has rights to a government funded patent for a drug candidate but is not making reasonable efforts to bring it to market, the company may be failing to meet the requirements to achieve practical application of the invention. These criteria are considered on a case-by-case basis by the agency in view of the facts presented in each case.

If NIH were to march-in, the grantee could appeal that decision through the Federal courts. Only after the company had lost all legal appeals could NIH grant a license to a second company, should there be one interested in developing a new version. Additionally, the drug could be covered by other patents that cover certain aspects of the drug, such as methods of making and administering it. In such instances, the march-in could be ineffective, because the original company could stop a new company from making the generic until the other patents expire.

After the court appeals and expiration of any other patents, a company would typically have to conduct clinical trials or otherwise establish equivalency with the brand drug to obtain U.S. Food and Drug Administration approval. The entire process, including administrative hearings, court appeals and new clinical trials, could take years before the new product reached the market. In the meantime, alternative therapies may have become available or the patent subject to march-in may have expired.

NIH has considered march-in on several occasions and was either able to work with parties to reach an agreement to address the issues raised, such as the case with CellPro and Fabrazyme, or decided that the march-in legal requirements were not met to march-in to address the public health and safety issues raised, such as was the case with Norvir.[3]

Question. The COVID–19 pandemic has impacted every major sector of the economy of the United States, including our nation's biomedical research. I have heard from countless universities across the state of Illinois about the impact that this pandemic has had on the medical research pipeline. From shuttered labs, to interrupted or delayed clinical trials, to unforeseen pandemic-related costs, they have estimated that this pandemic has caused over $10 billion in lost research. Last year, Senator Moran and I sent a bipartisan letter to Senate leadership, requesting at least $10 billion in additional funding to help make-up for the unforeseen disruptions and costs to medical research nationwide.

Dr. Collins, I am wondering if you can speak to the toll that the pandemic has taken on medical research nationwide and what Congress might be able to do to help.

Answer. The National Institutes of Health (NIH) remains deeply concerned and mindful about how the spread of coronavirus disease 2019 (COVID–19) has negatively affected the biomedical research enterprise.[4] Last summer, the NIH estimated it would cost at least $10 billion to restart labs which were forced to rapidly close. That original estimate proved overly optimistic as the pandemic subsequently continued, and as such, the NIH now estimates the financial impacts to be approximately $16 billion on the biomedical and behavioral research enterprise.

The estimates considered many factors:

—Key resources, such as animal colonies, cell lines and expired reagents that need to be re-established.

—Access to core facilities that was limited due to a backlog of requests.

—Delicate and complicated equipment that required recalibration and quality control testing prior to returning to routine use.

—Requirements for social distancing to protect staff and clinical trial participants coupled with anticipated reluctance by participants to travel, which slowed the rate of clinical trial accrual and progress and increased the cost of conducting trials.

In addition to the financial estimates, the NIH fielded two online surveys to objectively document COVID–19's impact on the extramural research workforce.[5] The main finding from the surveys was that the majority of respondents noted concerns

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[3] See ott.nih.gov/policy/policies-reports under NIH March-In Response.

[4] https://nexus.od.nih.gov/all/2020/11/04/continued-impact-of-covid-19-on-biomedical-research/.

[5] https://nexus.od.nih.gov/all/2020/10/05/encouraging-participation-in-upcoming-nih-surveys-to-identify-impacts- of-covid-19-on-extramural-research/.

about research functions, research productivity, and financial status.[6] Well into the pandemic, many NIH-supported research labs enforced social distancing, inherently restricting access and severely limiting the ability to generate research results and preliminary data at a crucial time in career development of early stage investigators and trainees. Junior faculty, often with only a single NIH award and unable to access their labs to generate additional data, are at risk of losing all funding and may have insufficient data to write papers while working from home. Some investigators, especially women with dependent care responsibilities, are more negatively affected. Investigators supported by training or career development awards are experiencing hiring freezes and job revocations, jeopardizing the ability of early-stage career investigators to transition to independence, particularly as they come to the end of their current funding. Clinical investigators have been diverted from their research labs to meet the clinical demands of COVID–19 patient care.

Considering these effects, the NIH is concerned about potential pandemic-related losses of scientists exiting the biomedical research workforce and abandoning scientific careers to seek alternative employment. In an effort to address the unanticipated impacts of the pandemic on the career trajectories of early career scientists, the NIH has provided several policy flexibilities, including grant award extensions (both funded and un-funded), opportunities for investigators to extend the timeline for early career status, provided administrative supplements, and more.

QUESTIONS SUBMITTED BY SENATOR BRIAN SCHATZ

Question. At the hearing, we discussed psychedelic drug research and the potential of these drugs to treat mental health illness. You stated that the NIH would consider having a workshop on this subject.

What is the current status of NIH-funded clinical trials involving human subjects on the potential benefits of psychedelics combined with psychotherapy?

Are there statutory or regulatory barriers to NIH pursuing or funding human subject research on psychedelic drugs?

When does NIH plan to convene a workshop on psychedelic drug research?

Answer. The National Institutes of Health (NIH) supports research on the development and testing of pharmacological interventions—including the use of hallucinogens such as ketamine, and psychedelic drugs such as psilocybin—for the treatment of illnesses. In particular, the National Institute of Mental Health (NIMH) requires an experimental therapeutic approach for the development and testing of therapeutic interventions for mental illnesses, in which the studies not only evaluate the clinical effect of an intervention, but also generate information about the mechanisms underlying a disorder or an intervention response. Research on psychedelic drugs holds promise for uncovering mechanisms of mental illnesses and possible interventions, ultimately leading to novel treatments with fewer side effects and lower abuse potential. Further research is needed to examine the efficacy and long-term safety of psychedelic drugs, including with repeated exposure and potential interactions with existing treatments.

The dissociative anesthetic ketamine has recently emerged as an effective fast-acting antidepressant.[7] The NIMH Director's Message, "New Hope for Treatment-Resistant Depression: Guessing Right on Ketamine," describes the role of NIMH and other researchers in the development of esketamine, a U.S. Food and Drug Administration-approved, rapid-acting medication that targets treatment-resistant depression.[8] Within the NIMH Intramural Research Program, Dr. Carlos Zarate is now conducting clinical trials to better understand how ketamine rapidly reduces depressive symptoms in people with treatment-resistant depression or bipolar depression.[9,10]

The National Institute on Drug Abuse (NIDA) currently supports a clinical trial which aims to assess the efficacy of ketamine, in combination with behavioral therapy, in the treatment of cocaine use disorders.[11]

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[6] https://nexus.od.nih.gov/all/2021/03/25/the-impact-of-the-covid-19-pandemic-on-the-extramural-scientific-workforce-outcomes-from-an-nih-led-survey/.

[7] pubmed.ncbi.nlm.nih.gov/27839782/.

[8] www.nimh.nih.gov/about/director/messages/2019/new-hope-for-treatment-resistant-depression-guessing-right-on- ketamine.

[9] clinicaltrials.gov/ct2/show/NCT03065335.

[10] clinicaltrials.gov/ct2/show/NCT03973268.

[11] clinicaltrials.gov/ct2/show/NCT03344419.

Additionally, a privately funded clinical trial is assessing the potential efficacy of the psychedelic drug psilocybin for the treatment of obsessive-compulsive disorder.[12] While the NIH is not directly funding this trial, NIMH does support the trial's principal investigator through a Mentored Patient-Oriented Career Development Award.[13]

Further, a number of NIH-funded researchers are conducting basic and preclinical research to investigate the use of psychedelic drugs as potential therapeutic interventions for mental illnesses. For example, NIMH-funded researchers are examining the mechanisms underlying the antidepressant effects of psychedelic drugs in an effort to develop novel, non-hallucinogenic treatment strategies that are both safer and more effective than existing treatment options.[14]

As with all human subjects research, clinical research on psychedelic drugs is governed by several statutes, regulations, and policies intended to protect the rights and welfare of research participants. For example, NIH has specific requirements for research staff and policies regarding research conduct, safety monitoring, and reporting of information about research progress.[15] In accepting an award that supports human subjects research, the recipient institution assumes responsibility for all research conducted under the award, including protection of human subjects at all participating and consortium sites.[16] All human subjects research must also be reviewed, approved, and monitored by an Institutional Review Board.[17]

Because psychedelic drugs are controlled substances, clinical research using psychedelic drugs must also follow Drug Enforcement Administration requirements, including registration, inspection, and certification of the drugs.[18]

From April through June 2021, the Trans-NIH Integrative Medicine Course Organizing Committee hosted a series of research talks on psychedelic drugs.[19] Building on these research talks, NIMH and NIDA are now working together to convene a scientific workshop in winter 2021. This workshop will bring together leading researchers to examine the state of the evidence for the use of psychedelics in the treatment of mental illnesses.

Question. The United States shares a unique political relationship with the Native Hawaiian community. Different Federal agencies within HHS are responsible for the administration of Native healthcare programs, but the same Federal trust responsibility requires the provision of comprehensive, quality healthcare to Native Hawaiians, Alaska Natives and American Indians. In 2015, NIH established the Tribal Health Research Office within the Office of the Director to coordinate tribal health research activities across NIH. However, no such research office exists for Native Hawaiians.

Would you consider expanding the scope of the Tribal Health Research Office to include Native Hawaiians? Would this help to increase the number of Native Hawaiian researchers and the amount of Native Hawaiian research being conducted across the country?

Has NIH set any goals for the Tribal Health Research Office, and how will you measure its success and impact across NIH's Institutes and Centers?

Some funding opportunities at NIH, such as the Native American Research Centers for Health program, do not permit entities serving Native Hawaiian communities to apply. Why are these entities excluded, and would NIH consider including these entities in the eligibility for these grant opportunities?

Answer. The National Institutes of Health (NIH) Tribal Health Research Office (THRO) does not conduct disparity research on Native American populations. THRO ensures that the NIH fulfills its obligations to Indian Tribes as federally recognized sovereign nations, conducts government to government interactions appropriately, and holds formal Consultations with Tribal governments on policy, regulatory, and legislative issues that have a significant direct impact on Indian Tribes.

The National Institutes of Health (NIH) published the NIH Strategic Plan for Tribal Health Research with input from American Indian/Alaska Native (AI/AN) Communities and the NIH Tribal Advisory Committee (TAC). The plan includes four agency-wide strategic goals: enhancing communication and collaboration; building research capacity for AI/AN communities; expanding research; and enhancing

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[12] clinicaltrials.gov/ct2/show/NCT03356483.
[13] reporter.nih.gov/project-details/10127338.
[14] reporter.nih.gov/project-details/10003396.
[15] grants.nih.gov/policy/humansubjects/policies-and-regulations.htm.
[16] grants.nih.gov/grants/policy/nihgps/html5/section__4/4.1.15__human__subjects__protections.htm.
[17] www.fda.gov/regulatory-information/search-fda-guidance-documents/institutional-review-boards-frequently-asked-questions.
[18] grants.nih.gov/grants/policy/nihgps/html5/section__4/4.1.5__controlled__substances.htm.
[19] events.cancer.gov/nci/psilocybinresearch/agenda.

cultural competency and community engagement. The Tribal Health Research Office (THRO), along with the NIH Institutes and Centers (ICs), developed processes and metrics for evaluating progress on the strategic objectives and their supporting action items to achieve these goals. THRO regularly collects data on AI/AN health research activities from all ICs through an automated process to analyze the NIH research portfolio, assess progress towards the strategic goals, and measure impact across NIH.

The National Institute of General Medical Sciences in conjunction with multiple NIH Institutes, Centers, and Offices (ICOs) partner with Indian Health Service (IHS) to support the Native American Research Centers for Health (NARCH). NARCH grant applications are submitted by and awarded to a tribe or tribal organization, who are sovereign nations with distinct governing bodies. Awarding the grant directly to the tribe or tribal organization allows for the community to dictate and oversee research priorities, while drawing upon necessary expertise from the research community to accomplish its scientific goals.

QUESTIONS SUBMITTED BY SENATOR JOE MANCHIN, III

Question. West Virginia is consistently ranked last in the nation for health outcomes. In 2020, the America's Health Rankings Report ranked West Virginia 50th for premature deaths, frequent mental distress, and multiple chronic conditions. We also rank last in life expectancy. West Virginia has, in many ways, been left behind as medical advances have saved lives in other places.

What is NIH doing to bridge this gap in health outcomes?

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

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

Answer. The National Institutes of Health (NIH) recognizes the unique health disparities that rural communities face, and as such, rural health is an important area of research for the agency.

Through diverse collaborations and partnerships with communities, academic institutions, and state agencies, NIH supports and conducts rural health research to improve health outcomes and reduce rural health disparities with a special emphasis on the poor in rural communities. In fiscal year 2020, NIH supported more than 1,000 rural health-related grants for approximately $728 million. In 2020, West Virginia received approximately $45.7 million in funding from NIH, of which about $6.4 million supported research and research capacity-building activities related to rural health.

In 2019, NIH held the Inaugural NIH Rural Health Seminar, a collaboration of several NIH Institutes and Centers to explore topics in rural health and opportunities for research collaborations to improve rural health outcomes. In 2020, NIH hosted a virtual rural health conference entitled, NIH Rural Health Seminar: Challenges in the Era of COVID–19. In October 2021, NIH will host the Pathways to Prevention Workshop: Improving Rural Health Through Telehealth-Guided Provider-to-Provider Communication, a virtual event to identify research gaps, explore barriers, and facilitate successful, sustainable implementation of provider-to-provider telehealth in rural settings.

NIH's rural health research focuses on key areas aimed at addressing health disparities that rural populations in West Virginia and around the United States experience. In fiscal year 2020, in response to the disproportionate impact of coronavirus disease 2019 (COVID–19) on racial and ethnic minority, and other vulnerable communities including rural populations, NIH established the Rapid Acceleration of Diagnostics for Underserved Populations (RADx-UP) initiative. The overreaching goal of the RADx-UP initiative is to understand the factors associated with disparities in COVID–19 morbidity and mortality and to lay the foundation to reduce disparities for those underserved and vulnerable populations more impacted by COVID–19. One example of a RADx-UP project in your state, is the Developing Novel Strategies to Increase COVID–19 Testing among Underserved and Vulnerable Populations in West Virginia through Community and State Partnerships. This project will implement collaborative strategies to increase availability and uptake of severe acute respiratory syndrome coronavirus 2 (SARS CoV–2) testing among the medically underserved, rural West Virginia population that includes multiple vulnerable groups at risk for severe COVID–19 and death. This initiative will test whether those implemented strategies, including home test kit and mobile unit mechanisms, successfully increase testing, and if not, determine why the interventions did not work to inform future sustainable testing policy.

In addition, NIH supports the West Virginia University Health Sciences TME CoBRE project, which focuses on the microenvironment of different tumor types, including cancers initiating in the bone marrow, head and neck, breast, and brain. This project will increase understanding of the constant interaction between the tumor and its environment, provide diverse training opportunities and mentoring strategies for junior faculty, and develop critical infrastructure and recruit additional tumor microenvironment focused scientists to West Virginia. Another project, the West Virginia Clinical and Translational Science Institute: Improving Health through Partnerships and Transformative Research (WVCTSI), leads statewide collaborations and innovation in clinical and translational research. This project will build sustainable research infrastructure, recruit clinician scientists and translational researchers that excel in team science, and actively engage with multiple stakeholders that include communities, medical providers, and policy makers to improve the health of West Virginians.

NIH is committed to ensuring that there are opportunities for poor rural Americans to access the benefits of research and that research addresses the unique strengths and challenges of rural communities by supporting several initiatives focused on human immunodeficiency virus (HIV), cardiovascular disease, cancer, drug addiction, and other chronic diseases disproportionately affecting rural communities. First announced in April 2018, the NIH Helping to End Addiction Longterm℠ Initiative, or NIH HEAL℠ Initiative, is an expansive agency-wide effort. It spans basic, translational, clinical, and implementation science and promotes collaborations of all types of research to address the crises of opioid misuse, addiction, and overdose in the United States. Launched in fiscal year 2020, Strategies to Improve Health Outcomes and Reduce Disparities in Rural Populations supports research to promote a greater understanding of the challenges faced by rural populations in developing or adapting evidence-based interventions that can reduce health risks faced by rural Americans. A total of eight awards were funded including: Harnessing the Power of Peer Navigation and mHealth to Reduce Health Disparities in Appalachia which is using a community-based approach to integrate peer navigation and mobile health strategies to develop a culturally congruent, bilingual intervention to increase the use of HIV, sexually transmitted infection, and Hepatitis C prevention and care services among individuals with health disparities living in rural Appalachia. Another study, Heart of the Family: A Cardiovascular Disease and Type 2 Diabetes Risk Reduction Intervention in High-Risk Rural Families is examining the effects of a family focused, lifestyle intervention that is culturally tailored for use with rural Hispanic or Latino and non-Hispanic or Latino adults. In 2020, the National Institute on Minority Health and Health Disparities (NIMHD) funded four rural Resource Hubs to focus on rural health research. These hubs will involve coalitions of researchers and community partners to build research capacity in an identified rural catchment area and offer opportunities to share resources and data across collaborators.

NIH continues to support the Accelerating Colorectal Cancer Screening and Follow-Up Through Implementation Science (ACCSIS) Program, a Cancer Moonshot? Initiative, designed to reduce cancer screening disparities. The aim is to identify evidence-based interventions and identify promising approaches for bringing these interventions to unscreened populations. Researchers test interventions such as mailing programs for home testing, provider education, and clinic-based patient navigation among Medicaid, rural, and racial and ethnic minority groups. In fiscal year 2020, NIH reissued and released the Pragmatic Research in Healthcare Settings to Improve Diabetes and Obesity Prevention and Care funding opportunity announcement. This initiative aims to improve diabetes and obesity prevention and/or treatment that are adapted for implementation in healthcare settings where individuals receive routine medical care. One of the funded grants, Telemedicine for Reach, Education, Access, Treatment and Ongoing Support (TREAT–ON), is a diabetes educator-driven, primary care-based telemedicine model that redesigns primary care practice to provide access to real-time ongoing support and help high risk participants in an underserved rural community to achieve and sustain improvements in clinical, psychosocial and behavioral outcomes. The NIH Minority Health and Health Disparities Strategic Plan 2021–2025 aims to test best practices for dissemination and implementation of minority health and health disparities research in diverse diseases and conditions into rural communities.

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

Question. The NIH funds the WV Clinical and Translational Science Institute at West Virginia University through a 5-year $20 million grant. The Institute provides critical health research across West Virginia and has successfully mentored early

career investigators, established pilot project funding, and created a research network across 27 primary care sites. Their research has focused on important health issues in my state including lung disease in coal miners, opioid addiction, and the hepatitis C epidemic, as well as cancer, heart disease, and stroke. Most recently, the Institute has been on the front line of COVID–19 research, having received a $1.5 million NIH Grant to lead an 8-state effort so that data from COVID–19 patients could be analyzed to develop the most impactful COVID–19 research. They're also responsible for utilizing the NIH RADx grant to scale up COVID–19 testing in WV Communities.

Can you comment on the importance of continued collaboration between the NIH and research institutions like the WV Clinical and Translational Science Institute at West Virginia University?

What more can we be doing to support young researchers, such as those mentored through this Institute?

Answer. One of the core programs supported by the National Institute of General Medical Sciences (NIGMS) Institutional Development Award (IDeA) is the IDeA Networks for Clinical and Translational Research (IDeA–CTRs), which includes the West Virginia Clinical and Translational Science Institute (WV CTSI). The IDeA–CTR network aims to:

—Support the development and/or enhancement of infrastructure and human resources required to address clinical and translational research needs in IDeA-eligible states and jurisdictions;

—Strengthen clinical and translational research that addresses the broad spectrum of health challenges faced by populations in IDeA-eligible regions; and

—Foster and coordinate collaboration in clinical and translational research within an IDeA-CTR network and with other institutions.

Strengthening and expanding the capacity for clinical and translational research in IDeA-eligible states is a pressing need, since health conditions such as obesity, diabetes, cardiovascular diseases, cancer, infectious diseases, chronic obstructive pulmonary disease, maternal health issues, and substance use disorders are disproportionally present in and borne by communities in these states. The IDeA–CTR networks support health research professionals who have first-hand knowledge of these challenges in order to understand and improve the health outcomes of residents in affected jurisdictions. Having the WV CTSI in place during the coronavirus disease 2019 (COVID–19) pandemic, for instance, has allowed it to act as a springboard for West-Virginia-based research aimed at studying and addressing the virus. The $1.5 million supplemental award referenced in this question facilitated the development of an eight-state consortium that created an IDeA State COVID–19 Patient Registry. Through the collaboration between the NIH and WVU, the Registry has become a key component of the National COVID Cohort Collaborative, making important contributions in addressing the unique challenges brought by COVID–19 to traditionally underserved groups such as rural populations. Another supplement to the WV CTSI supports a network for conducting COVID–19 testing in West Virginia that includes the state health department, the national guard, and rural clinics. This collaborative effort is playing a major role in facilitating the state's testing efforts. Finally, the WV CTSI is also a key participant of an NIH-sponsored multisite Post-Acute Sequelae of SARS–CoV–2 (PASC) study of "Long COVID" patients who continue to experience symptoms long after initial infection.

Both NIGMS and NIH remain committed to supporting IDeA–CTR networks like the WV CTSI, given the very important role that such networks play in developing research infrastructure and improving health outcomes within IDeA states.

The National Institutes of Health (NIH) believes that supporting early career researchers is crucial to maintaining a productive, innovative, and diverse biomedical research workforce that can continue to advance the vitality of the scientific research enterprise. NIH's Next Generation Researchers Initiative (NGRI) is developing and implementing strategies to identify, support and retain investigators across early career stages.

As part of the NGRI, NIGMS has prioritized and included several strategies for supporting trainees and early-stage investigators (ESIs) within its 2021–2025 Strategic Plan, along with targets for implementing those strategies that provide accountability and the ability to measure progress. Career development initiatives such as the recently launched Maximizing Opportunities for Scientific and Academic Independent Careers (MOSAIC) program focus on retaining and supporting postdoctoral scholars from diverse backgrounds through the critical point of transitioning them into independent faculty careers. Cooperative agreements with professional organizations support educational activities that equip MOSAIC scholars with professional skills, mentoring, and career networks. At the individual level, grants such as NIGMS' Maximizing Investigators' Research Award (MIRA) offer

support to early-stage investigators (ESIs) by providing them both the opportunity to perform creative and ambitious research as well as the flexibility to follow important new research directions and scientific insights. Since launching this award mechanism in 2015, MIRA has supported 628 early-stage investigators (ESIs), at least two of whom were in West Virginia. In fiscal year 2020 alone, NIGMS funded 200 ESIs through MIRA. As these examples illustrate, both the NIGMS and NIH remain committed to supporting promising early career investigators in every state in the nation.

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

Question. Dr. Collins, I am a big supporter of the Clinical and Translational Science Award (CTSA) program. I believe we should look for ways to strengthen the CTSA program and reinforce the hubs around the country. That is why I am troubled to hear about a possible CTSA reorganization that will be announced in June. This reorganization comes with limited discussion and consultation with the CTSA directors. I am concerned, specifically, with the proposal to break up hub awards into smaller pieces, requiring CTSAs to write several grant applications instead of just one. Dr. Collins, I have two questions. First, as you know, this Committee pays a lot of attention to CTSAs and has been concerned in the past about communication between NCATS and the CTSA community. For example, NCATS emailed relevant stakeholders to combat the rumors about changes to the CTSAs, but did not provide any relevant data to explain what they want to do and why they want to do it. That did nothing but add to the concerns and speculation in the community.

Why haven't these specific changes been discussed broadly within the CTSA community? I believe if there was open dialogue and a stronger partnership between NCATS and CTSAs, there would likely be more buy-in from the community.

Two, how does cutting the hub award and requiring CTSAs to compete for multiple awards strengthen the program? It appears to me that this change would bring uncertainty to the program and jeopardize the stability of the hubs.

Answer. The Clinical and Translational Sciences Award (CTSA) program is indeed a very valuable and important program for the National Center for Advancing Translational Sciences (NCATS), NIH, and the nation. NCATS understands that there are often concerns when there are planned updates to a program, particularly one as large and impactful as the CTSA Program. The planned updates are part of the regular NIH business process for reissuing Funding Opportunity Announcements (FOAs), which is required because FOAs expire after 3–4 years. The planned updates will maintain the structure of the program and reflect the public input received—much of which was provided by the CTSA hub institutions and investigators. The planned updates are designed to strengthen the program, by prioritizing hub strengths, streamlining the overall application process, emphasizing clinical partnerships which are critical to achieving the objectives of this national program, and stabilizing the funding provided to the hub institutions by allowing up to 7 years of funding (rather than the typical five-year award period for NIH awards).

How NCATS Engages with the CTSA Community: NCATS agrees that a strong partnership is extremely important and works closely with the CTSA community on a regular basis.

—*Regular Meetings:* A CTSA Steering Committee[20] including leadership from NCATS and the CTSA Principal Investigator community, meets monthly. A monthly webinar for all CTSA Program investigators also shares information about the program. NCATS CTSA leadership and program officers also routinely engage with investigators and institutional leadership across the CTSA Program as part of their regular duties for implementing a program of this size and complexity. In addition, there are yearly multi-day conferences where the CTSA investigators and NCATS staff engage deeply on important issues related to the CTSA program.

—*Engaging the Community on Updates to the Planned FOA:* To maintain fair and open competition for funding opportunities, NCATS cannot discuss specific details about a draft FOA with select groups of the public, particularly those who already have funding and would be re-competing for the funds. The level of engagement must be framed to ensure that all investigators and institutions, not only the current awardees, have an equal opportunity to compete for the program funds and that NCATS officials act impartially and not give preferential treatment to any organization or individual.[21] In following these NIH policies,

[20] clic-ctsa.org/groups/steering-committee.

[21] ethics.od.nih.gov/principles-ethical-conduct-government-officers-and-employees.

NCATS provided multiple opportunities to ask for and receive input from the broader public, including the CTSA community, on how to improve the CTSA Program.

—A key approach for input was a Request for Information (RFI) released in the Fall of 2019. The comments received, many from the CTSA community, significantly influenced the updates to the CTSA Program that NCATS is planning. (RFI; NOT–TR–19–027 [22])

—General feedback was sought from CTSA application peer reviewers over multiple study sections; many of whom are also CTSA investigators.

—Informal discussions occurred with CTSA Program consortium members, individually and in small group settings, over the course of typical program oversight and interactions.

—Often the first public discussion about a future FOA occurs when NCATS, like other NIH Institutes and Centers, seeks concept approval from its Advisory Council during a session open to the public. This occurs on June 11, 2021. Of note, the NCATS Advisory Council includes three members that are Principal Investigators from the CTSA Program.

—In addition, NCATS has built in additional time after the release of the new FOA—6 months, instead of 2–4 months, prior to the first application receipt date—to familiarize all potential applicants with the new FOA, including hosting of webinars to provide technical assistance to the applicant community.

—NCATS widely shared a communication to address inaccuracies and rumors about changes to the CTSA Program FOA. The letter did not discuss planned changes to the CTSA Program nor provide data, as sharing details about the FOA in a non-public manner prior to its posting is not permissible.

—Summary of Stakeholder Feedback: From the input received through the multiple approaches described above, stakeholder feedback centered around four distinct areas: (1) decreasing application administrative burden, (2) increasing Hub flexibility and Hub specialization opportunities, (3) expanding Hub funding options, and (4) preserving partnerships and collaborations. Three additional areas were identified by NCATS for improvement: (1) ensuring the CTSA Program's sustainability (in terms of avoiding the need to reduce the number of hubs or cut budgets), which requires updates to budget formulas and calculations; (2) increased emphasis towards addressing health disparities; and (3) strengthening clinical research capabilities, which have been critical to the national responses to the opioid epidemic and the coronavirus disease 2019 (COVID–19) pandemic.

Hub Budgeting: NCATS takes the proper stewardship of taxpayer funds very seriously. NCATS does not intend to change the number of hubs or the amount of funding dedicated to the hub core awards. Future award amounts will be based on the amount requested by each applicant and will follow a revised formula for classifying the size of awards from what is currently used. In addition to incorporating feedback from different stakeholders, one of NCATS' objectives is to ensure the long-term sustainability of the program while avoiding a reduction in the number of hubs or reducing hub budgets to stay within the appropriated budget for the program. Requested budgets for CTSA awardees have been increasing to the highest award size under the CTSA graduated award structure, which is not sustainable under current funding for the program, so a restructured award calculation is needed. The total award size of future hubs is anticipated to be similar to the current awards for the vast majority of awardees.

Structure of the Program Applications: NCATS considered extensive public feedback, outlined above, in updating the CTSA Program FOA, including how these updates could contribute to stabilization for the awardees and to sustainability of the program. To date, the application process for institutions applying for CTSA hub awards has been complicated and burdensome, linking up to three separate activities together into one package, the U54 application. Linking the Hub, Career Development, and Training activities together for application submission and peer review is primarily for the benefit of NIH in being able to track these activities. However, based on feedback, it places substantial burden on the applying institution in the form of developing large, complex applications, often containing several areas of duplicate information. The review of three separate activities in one application risks pulling an institution out of funding range, due to one of the activities not faring well in peer review. Applicants that do not successfully compete face a prolonged period of uncertainty for funding, while having to address, revise, and resubmit the

[22] grants.nih.gov/grants/guide/notice-files/NOT-TR-19-027.html; (see this video,www.youtube.com/watch?v=LDBJSl-__QbQ, for an overview presentation of feedback received).

entire U54 application package for a subsequent review cycle. These factors combined with the duration of the awards—five years —raises the stakes of each application and contributes to an environment where applying and awarded institutions are in a constant state of application preparation.

Stakeholder concerns about the complexity of the current application are an important and consistent piece of feedback NCATS received. Separating the applications will streamline the submission process for each component, will reduce duplication of information in an application, will result in less reliance on the success of one part of the application, will avoid the risk of significant delays in awarding a hub if the Training or Career Development components are not strong, and may allow better alignment of Training and Career Development awards with the clinical training calendar. Separating the Hub application from the training and career development applications will also allow the Hub application, which is the key institutional award, to be awarded for up to 7 years, more than the standard 5 years. With this strategy, NCATS intends to provide further stability to an institution's funding by extending the Hub award. Combining all applications together does not allow for that seven-year Hub award option, as NIH limits training and career development awards to 5 years. Separating the applications and providing the additional planned funding opportunities will also give the institutions more control over where they place their priorities based on their own strengths, another key piece of feedback received through stakeholder input.

In closing, we hope that these responses have addressed your concerns. If not, NCATS is happy to provide additional information. NCATS recognizes the significance of the CTSA Program. The pandemic has further served to highlight the importance of this program in responding to emerging clinical and translational needs at local, regional, and national levels. NCATS' intent with the proposed updates to the CTSA FOA is to strengthen the program, provide additional funding stability, and continue to incorporate research to tackle health disparities through this program. NCATS also wants to address important concerns raised by the CTSA community to streamline application and award preparation processes, continue to emphasize the importance of partnerships, and allow institutions more flexibility to leverage their strengths in contributing to this important national resource.

Question. Dr. Collins, the impact of COVID–19 has been significant—both to Americans physical health, but also to their mental health. The fiscal year 2022 budget includes $25 million for focused research on the impact of the pandemic on mental health.

Can you discuss what research areas this funding will be focused on and how the All of Us research initiative will play a role in understanding the full impact of the pandemic?

Answer. The All of Us Research Program's participants come from diverse communities across the United States and generously donate their data and time to drive a wide range of biomedical discoveries, which are vital for informing public health strategies and preparedness. Due to the diverse nature of the program, the All of Us Research Program will play a vital role in understanding the mental and physical impact of the pandemic across the United States and within some of the hardest-hit communities. All of Us began to address the challenge of the coronavirus disease 2019 (COVID–19) pandemic in May 2020 by leveraging its significant and diverse participant base to seek new insights into COVID–19 and its impact through an online COVID–19 Participant Experience (COPE) survey.[23,24] The COPE surveys focused on understanding the mental and physical impacts of the COVID–19 pandemic on participants and included questions on symptoms, stress, social distancing, social determinants of health, and economic impacts. Participants were invited to take the survey in May, June, July, November, and December 2020, and February 2021. This multi-pronged assessment will enable researchers to study the effects of COVID–19 over time and better understand how COVID–19 affects people's mental and physical health differently. To date, over 10,000 participants completed all six COPE surveys and over 100,000 completed at least one COPE survey during the pandemic, with 70 percent of those participants coming from a community that is historically underrepresented in biomedical research.

In addition to COPE, All of Us tested blood samples from over 24,000 participants collected between January 2 and March 18, 2020, for the presence of SARS–CoV–2 antibodies, which provided evidence of infection in five states prior to initial reports. The program anticipates making the full results of this study available in

[23] allofus.nih.gov/news-events-and-media/announcements/all-us-research-program-launches-covid-19-research- initiatives.

[24] www.nlm.nih.gov/dr2/COPE__Survey__NIH__All__of__Us__Clean__4.27.20.pdf.

June 2021.[25] Additionally, All of Us is collecting relevant electronic health record (EHR) information from more than 246,000 participants, some of whom have been diagnosed with COVID–19 or sought healthcare for related symptoms, to help researchers look for patterns and learn more about the physical and mental health impacts of COVID–19 and the effects of different medicines and treatment. As data are made available from all of these efforts, researchers will look for new leads that may bring greater precision to the diagnosis, treatment, and prevention of COVID–19, including those communities that have been hit the hardest. The program will make data gathered through these activities broadly accessible to approved researchers on a rolling basis, in future releases of its secure data platform, the Researcher Workbench.[26] The program will continue to explore additional ways it can leverage its unique and diverse dataset to answer critical research questions to enhance our understanding about the full impact of the pandemic, especially with a focus on mental health.

Question. Dr. Collins, the COVID–19 pandemic highlighted the need to use nonhuman primates (NSP) in research. The budget requests $30 million for NSP infrastructure.

Can you provide further details to the Committee on the need for this funding and details on how this funding would be allocated and to whom?

What types of research would be at jeopardy if NSPs were not replaced or expanded?

Answer. The National Institutes of Health (NIH) remains committed to protecting animal welfare while, at the same time, advancing biomedical research and human health. The budget request for $30 million for nonhuman primate infrastructure would cover facilities used to house nonhuman primates which require continual updates and maintenance to ensure responsible stewardship over these invaluable resources. The funds in the budget request would be distributed by soliciting applications from NIH grantees to improve existing facilities, not to establish new nonhuman primate facilities. Several nonhuman primate facilities have existed for over 60 years and housing enclosures require frequent repair and replacement. New construction for research facilities would include animal holding rooms, necessary equipment such as surgical tables, centrifuge, ultrasound, clinical analyzer, procedure, and veterinary clinical support in order to meet or exceed the current high-level care of the nonhuman primates. Additionally, the COVID–19 pandemic highlighted the need for new construction to expand animal biosafety level 3 areas in order to have biocontainment facilities associated with nonhuman primate facilities. In addition to ethically appropriate housing, nonhuman primates require a proper diet, clinical/veterinary care as well as psychological and environmental enrichment, which necessitates skilled staff and additional resources including supplemental produce, various enrichment devices such as foraging devices for food, various toys, and puzzles.

NIH would support expansion at existing NIH-supported facilities to leverage the investment. The NIH Office of Research Infrastructure and Programs (ORIP) supports a well-coordinated national consortium of seven National Primate Research Centers (NPRCs) and other breeding colonies that collectively address research needs and trends, best husbandry practices, maintenance of genetic diversity, standardization of models, ethics, rigor, and reproducibility. NPRCs are national resources serving not only NIH-funded investigators but other federally funded investigators, foundations, and industry, including many SARS–CoV–2 projects in the last year.

Research with animal species, including nonhuman primates, remains critical for modeling human physiology and is essential for developing new prevention strategies, treatments, and cures for disease beyond the need for responding to emerging infectious diseases. Nonhuman primates have been essential for understanding human biology and developing treatments for diseases, mostly because of our shared anatomy, physiology, and behavior. Importantly, the genetic sequence similarities between nonhuman primates and humans can reach up to 98.77 percent, which has made nonhuman primates models critical for studying neurobiology, transplant tolerance and rejection, infectious diseases, reproductive biology, and regenerative medicine. More recent applications have been in regenerative medicine and gene therapy and editing. There is a rapidly emerging need for marmosets in the neurosciences where recent National Academies of Sciences, Engineering, and Medicine (NASEM) reports and the Brain Research Through Advancing Innovative

[25] The results of this study were announced on June 15, 2021; complete details at: allofus.nih.gov/news-events-and-media/announcements/nih-study-offers-new-evidence-early-sars-cov-2-infections-us.

[26] www.researchallofus.org/.

Neurotechnologies® (BRAIN) Initiative community have pointed out that demand far exceeds supply.[27] Another critical area of intense need and research development is nonhuman primate models of Alzheimer's disease to develop therapies. Nonhuman primate models are commonly used for studies of visual systems, auditory systems, cognitive function, and brain connectivity. The single largest application of nonhuman primates continues to be in developing vaccines and therapies for HIV/AIDS.

Research using animal models, including nonhuman primate models, has led to tremendous advances critical for saving countless lives and extending human life expectancy around the world. Until suitable non-animal models are developed, the complexity of human systems, both in health and in disease, can only be truly understood through complementary model systems with sufficient complexity, and nonhuman primates remain invaluable for this effort. When animal models are required, NIH will only conduct and support research in accordance with the highest scientific and ethical principles. To uphold these principles, the NIH budget includes investments in nonhuman primate facilities, resources, and enrichment.

Question. Dr. Collins, how much funding, broken down by Institute or Center, has NIH repurposed for COVID–19 related lab reopenings or lost research activities?

Answer. To support our recipients affected by the pandemic, the National Institutes of Health (NIH) provided extensions, both funded and unfunded, as well as administrative supplements, to address the unanticipated impacts of the pandemic. The NIH has also issued multiple funding opportunities for current recipients to repurpose existing awards and expand the scope of ongoing research to include coronavirus disease 2019 (COVID–19) research activities.[28] Continued support for these projects is contingent on satisfactory progress, the availability of funds, and NIH Institute and Center (IC) funding priorities, which continue to change as the pandemic, and research on COVID–19 progresses.

Decisions related to individual awards are made by the funding NIH IC on a case-by-case basis, taking into account those critical factors. All requests to change the scope of an NIH grant award require prior approval from the awarding NIH IC, as stipulated in the NIH Grants Policy Statement, section 8.1.2.5.[29]

The NIH continues to analyze the data on the impact of COVID–19 on the biomedical research community, and its potential impact on NIH budget and grant activities.

Question. It is my understanding that one of the main issues NIH faced related to COVID–19 expenses was for post-doctoral candidates finishing their training, research, or fellowship.

How has this issue been addressed and do you expect to see a funding issue related to the extension of some of these grant awards into fiscal year 2022?

Answer. The coronavirus disease 2019 (COVID–19) pandemic, along with extensive mitigation measures, has adversely affected progress in many biomedical research settings. Evidence from multiple sources, including results from a survey during the fall of 2020, indicates legitimate concerns about career trajectory for early career scientists.[30] Hearing these concerns, the National Institutes of Health (NIH) issued a Guide Notice detailing our approach to support early career scientists whose career trajectories may have been significantly affected by the pandemic.[31] Specifically, NIH is providing an opportunity for recipients in their last year of NIH Fellowship (F) and NIH Career Development (K) awards who have been impacted by COVID–19 to request extensions.[32] Such extensions will be considered on a case-by-case basis, within the existing availability of funds.

Generally speaking, the NIH typically makes between 500 to 600 F and K extensions per year, the vast majority (more than 95 percent) of which are no-cost extensions. Only seven funded extensions were awarded in fiscal year 2019. In fiscal year 2020, the NIH awarded 548 extensions, with 75 (14 percent) of these being funded extensions. Thus far in fiscal year 2021, 15 funded extensions are linked to NOT–OD–21–052, but we will have a much better sense of uptake as the fiscal year concludes. Though there appears to be a relative increase in the number of funded extensions commensurate with the pandemic, the absolute numbers remain low.

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[27] www.nap.edu/read/25356/chapter/7.

[28] grants.nih.gov/grants/guide/COVID-Related.cfm.

[29] grants.nih.gov/grants/policy/nihgps/HTML5/section__8/8.1.2__prior__approval__requirements.htm#Change4.

[30] nexus.od.nih.gov/all/2021/03/25/the-impact-of-the-covid-19-pandemic-on-the-extramural-scientific-workforce-outcomes-from-an-nih-led-survey/.

[31] grants.nih.gov/grants/guide/notice-files/NOT-OD-21-052.html.

[32] https://nexus.od.nih.gov/all/2021/02/08/extensions-for-early-career-scientists-whose-career-trajectories-have-been-significantly-impacted-by-covid-19/.

QUESTIONS SUBMITTED BY SENATOR CINDY HYDE-SMITH

Question. What is the fully intended scope of ARPA–H? Will it address diseases beyond cancer, diabetes, and Alzheimer's, such as ones with more challenging markets? Do you have examples?

Answer. The scope of the Advanced Research Projects Agency for Health (ARPA–H) is intended to be broad and, indeed, stretch beyond the areas initially identified by the President. There are a number of areas with substantial unmet needs—some examples include emerging infectious disease, rare and ultra-rare disease, and antimicrobial resistance—and, with targeted investments over time, breakthrough progress could be made. In addition to specific disease areas, ARPA–H intends to build capabilities and explore various platform technological approaches which may have broad applicability across a range of diseases and conditions. A recent commentary in Science [33] outlined some exciting concepts such as developing mRNA vaccines to prevent most cancers; creating molecular "zip codes" to more precisely target tissues and cell types while minimizing side effects; deploying holistic interventions that identify those at high-risk and leverage new telehealth approaches to eliminate racial disparities in maternal morbidity and mortality rates and premature births; and developing small, highly accurate, inexpensive, non-intrusive, wearable 24/7 monitors for blood pressure and blood sugar. While these examples are meant to illustrate the breadth of potential projects that ARPA–H could support, we believe it is projects like these that can have a significant impact for patients who are relying on biomedical research and innovation to live longer, healthier lives.

Question. Additionally, how will ARPA–H fit into the larger health focused R&D structure? How will its role be defined as unique among the various funding programs, and will there be coordination with other entities such as BARDA to ensure cooperation and avoid duplication?

Answer. The Advanced Research Projects Agency for Health (ARPA–H) is meant to become an integral component of the constellation of agencies focused on promoting health and research and development—both within and beyond NIH and HHS. As described in a recently published commentary in Science,[34] ARPA–H should be housed as a new entity within NIH. The rationale for this organizing principle is two-fold. First, the goals of ARPA–H fall squarely within the mission of the NIH, which 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." Second, the NIH offers a rich source of fundamental health research that will be foundational for a constructive, collaborative, and productive relationship with ARPA–H. We envision robust collaborations on synergistic topics with the existing NIH Institutes and Centers, along with organizations both outside and within the government. The added benefit of housing ARPA–H within NIH is that it will create administrative efficiencies so that more resources can be directed toward the mission and help avert duplication of effort.

In mid-July, the Administration launched a Federal Joint Fast Track Action Committee (FTAC) intended to help steer the creation of ARPA–H and lay the groundwork for strong interagency coordination. OSTP and NIH serve as co-chairs of this committee that includes representatives from the Department of Agriculture, DARPA, Office of the Under Secretary of Defense for Research & Engineering, ARPA–E, BARDA, CDC, CMS, FDA, VA, EPA, NSF, and the Smithsonian Institution, among others. Bringing these entities together at an early stage will help ensure strong collaboration and coordination among the various research-focused organizations throughout the Federal Government. The agency personnel who sit on the FTAC will also be a valuable source of insight and advice as ARPA–H is launched.

QUESTIONS SUBMITTED BY SENATOR PATRICK J. LEAHY

Question. I strongly support the Administration's renewed approach to innovation in medical research through the establishment of the Advanced Research Projects Agency for Health (ARPA–H). COVID–19 has shown that a commitment to breakthrough innovation, directed allocation of resources, and collaborative approaches can accelerate how scientific breakthroughs can be transitioned to treatments and cures. The administration has proposed that the agency will focus on innovative treatments in cancer, Alzheimer's disease, and opioid disorders. Several institutions in Vermont are national leaders in these stated research fields despite their smaller and more rural nature. While I strongly support any efforts to accelerate innovation,

[33] science.sciencemag.org/content/373/6551/165.
[34] science.sciencemag.org/content/373/6551/165.

I am concerned that valuable collaborators could be left out or lose out on Federal funding, particularly if there is no traditional grant application process.

What role will smaller and more rural research institutes play in ARPA–H? If projects are funded outside a grant application process, will there be established guidelines to include collaborators from rural or traditionally underrepresented areas?

Answer. Over the long term, the proposed structure for the Advanced Research Projects Agency for Health (ARPA–H) is intended to empower the ARPA–H leadership and staff to set and execute on research priorities for a variety of high-risk, high-reward, milestone-driven projects that can lead to novel capabilities, platforms, and resources that are applicable to a range of diseases. These priorities include the opportunity to fund smaller and more rural research institutes.

For the initial direction, the Administration is working to set up multiple pathways, both within the government and the broader stakeholder community, for priority setting and for exploring new areas ripe for research at ARPA–H. At the time of this hearing, the White House Office of Science and Technology Policy (OSTP) and the National Institutes of Health (NIH) are in the planning phases of convening multiple listening sessions with key stakeholder groups including patient organizations, industry, venture capitalists and philanthropists, and others from the academic and research communities. During these sessions, stakeholders will be asked to offer their perspective on what they see as the greatest research challenges and opportunities that could be addressed using the ARPA–H model. This input will help refine the scope and provide a wealth of ideas for the first ARPA–H director to consider as they develop the agency's vision.

In mid-July, the Administration established a Joint Fast Track Action Committee (FTAC) to help steer the creation of ARPA–H and lay the groundwork for strong interagency coordination. OSTP and NIH serve as co-chairs of this committee that includes representatives from Department of Agriculture, DARPA, Office of the Under Secretary of Defense for Research & Engineering, ARPA–E, BARDA, CDC, CMS, FDA, VA, EPA, NSF, and the Smithsonian Institution, among others.

Soliciting a diversity of perspectives and approaches will be a key tenet of the Advanced Research Projects Agency for Health (ARPA–H). Much like DARPA and ARPA–E, it will do so by supporting the best strategies to solve an identified challenge and by pursuing multiple approaches. Program managers will also have the authority to combine proposals from different institutions to assemble the boldest, most innovative portfolio, allowing each team to build on their strengths while benefiting from the knowledge, expertise, and resources from other institutions. ARPA–H will also provide awards that range in size and mechanism—from smaller, pilot projects to develop a prototype, to complex multi-site trials, to prizes that stimulate healthy competition and ingenuity. Further, ARPA–H will support a Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) program with business development, commercialization, and other resources to provide small businesses with the tools they need to be successful. These approaches are examples of mechanisms that ARPA–H will utilize to support a range of organizations across the country which may include small and/or rural institutions, and its portfolio will be regularly evaluated to ensure there is diversity of perspective. Because ARPA–H will be a nimble, dynamic organization, it will be able to readily pivot to experiment with new approaches.

Question. Chronic pain is a significant public health issue affecting an estimated 50.2 million Americans each year. Based on data from the National Health Interview Survey (NHIS), the total value of lost productivity due to chronic pain is estimated to be nearly $300 billion annually. 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. Scientific research suggests that long term use of such medications can result in the body's reduction of its own ability to fight pain. Even for patients who do not experience direct abuse or addiction with long term use, scientists have found that withdrawal symptoms are present when patients stop taking these medications. Unfortunately, research into addiction and alternatives to treatment has historically lagged at NIH. Enhanced research on chronic pain management and treatment, other than through the use of highly addictive opioid painkillers, has the potential to reduce substance abuse and promote better methods for addressing pain.

I strongly support the NIH Heal Initiative to find solutions to curb the national opioid public health crisis by understanding, managing, and treating pain. Please describe any progress made by the HEAL Initiative on medication development to alleviate pain and to treat addiction. What remains the biggest barrier to research to investigate new and alternative options to treat chronic pain?

Answer. The National Institutes of Health (NIH) recognizes the need to improve pain management without risk of addiction and other serious side effects. NIH is taking a multi-pronged approach to develop safe and effective therapies to reduce our reliance on opioids and treat addiction. The NIH Helping to End Addiction Long-term (HEAL) Initiative launched in 2018 has awarded over $1.5 billion for research to discover and accelerate development of non-addictive pharmacological and non-pharmacological pain treatments, as well as treatments for opioid use disorder (OUD) and overdose.

Through the HEAL Initiative, NIH supports over 70 targeted studies to accelerate the development of treatments for OUD, including novel medications and biologic agents, as well as novel formulations of approved medications to treat OUD and prevent opioid overdose. To date, 16 Investigational New Drug Applications were filed with the U.S. Food and Drug Administration and authorized to proceed for human studies. These studies focus on a variety of drug targets, as well as vaccines that could prevent opioids from entering the brain. HEAL currently funds nine opioid vaccine projects including vaccine candidates targeting oxycodone,[35] fentanyl[36] and heroin.[37] This strategy could offer more accessible, manageable treatment through longer-lasting vaccines to reduce the risk of relapse.

HEAL-supported work also includes studies to identify, optimize and test promising molecules, biologics, and devices for treating pain that target non-opioid pathways in the nervous system. Biomarker studies to enhance clinical trials and improve best practices are moving forward. In addition, non-pharmacological approaches to manage many different pain conditions are being evaluated through effectiveness and implementation research approaches.

In these ways, HEAL is providing much needed resources to advance research on new and safe alternatives to opioids for chronic pain. The complexity and diverse nature of chronic pain itself along with a high prevalence of other co-occurring chronic conditions such as diabetes, depression, and autoimmune disorders create an enormous challenge for advancing research.

Mechanisms for the causes of different pain conditions vary, biomarkers for patient response to treatment and likelihood for progression of disease also are characteristic of the disease condition. In addition, treatments for co-morbidities require careful balancing and often long- term multidisciplinary care. These and other factors require an expanded breadth and scope of pain research to better provide personalized care for those with chronic pain. The Federal Pain Research Strategy[38] describes research priorities to relieve the burden of pain. The NIH HEAL initiative provided support to move many of the report's recommendations forward.

Specifically, the NIH HEAL initiative established essential pain research infrastructure to accelerate development of new medications and devices to treat pain. An analgesic screening platform uses animal and human cell-based models such as neural tissue chips for rapid screening of molecules or devices for analgesic-relevant biological and pain behavioral activity. HEAL, with input from academic and industry partners, established an Early Phase Pain Investigation Clinical research network (phase 2 studies) to test safety and efficacy of novel therapeutics and a later stage pain management Effectiveness Research Network (ERN) to compare effectiveness of pharmacological and non-pharmacological approaches in many different pain conditions. The Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid Prescribing (PRISM) network focuses on clinical trials of non-pharmacologic pain therapies in healthcare systems. The Phase 2 network will launch trials on two new analgesics in late 2021. The ERN is supporting eight large trials for various pain management strategies. PRISM is supporting six large trials in healthcare systems. In addition, HEAL established an analgesic development pipeline to accelerate the development and testing of novel drugs and devices. This comprehensive program uses team-based science coupled with a comprehensive set of research resources to bring new therapeutics rapidly to the clinic. To advance the discovery and validation of new drug targets, HEAL has funded over 30 projects to discover and verify a diverse set of drug target types across multiple pain conditions, six drug optimization studies on new safe and effective pain treatments, and 11 projects to test the effectiveness of implanted devices and noninvasive stimulation of nerves in the brain or throughout the body to reduce perception of pain. In addition, to improve the efficacy of clinical trials for pain treatments, and to increase the chance that new therapeutics will advance along the regulatory path to approval, HEAL tests the development of biomarkers to objectively measure pain,

[35] reporter.nih.gov/search/Pcd2IghkPU6lnJkOT7FlFQ/project-details/9778811.
[36] reporter.nih.gov/search/Wp__sHzUhIUuYqDimSa90iw/project-details/9737173.
[37] reporter.nih.gov/search/GNnJWbYvQUeIlbwhgFofXA/project-details/9734921.
[38] www.iprcc.nih.gov/federal-pain-research-strategy-overview.

including pain associated with sickle cell disease, musculoskeletal disease, nerve pain and headache. Promising biomarkers identified through this program may advance to clinical validation through the Early Phase Pain Investigation Clinical Network (EPPIC-Net). Findings from these studies could improve quality of life for millions of people in the United States who experience pain daily. Recent HEAL accomplishments toward new therapeutics include two patent filings for small molecule modulators of pain receptors involved in chronic pain and migraine.

New directions for HEAL will also continue to pursue goals laid out in the Federal Pain Research Strategy,[39] including demonstration projects to aid in the development of a coordinated approach to pain management in healthcare systems. This effort would assess multi-disciplinary and multimodal approaches to pain management embedded in healthcare systems. Research within systems of pain care would allow for effective interventions to be adopted into the healthcare system and improve access for patients. Focused discussion with select healthcare program leadership would identify pain conditions of greatest opportunity, with an emphasis on effectiveness research, quality management and team-based care. This effort would seek to leverage existing infrastructure through ongoing collaborative and interagency efforts.

Another specific effort in development aims to advance health equity to address the wide disparities in care and treatment for pain and addiction, known to result in both the undertreatment and overtreatment with opioids, increased risk of addiction and overdose, lack of access to effective non-pharmacological options for pain treatment, and lack of access to evidence-based addiction care. Disparities in pain management exist across multiple levels: pain assessment, treatment, and management at the patient, provider, community, and healthcare system levels. Planned expansion to HEAL includes the development and implementation of culturally appropriate interventions for the prevention and management of pain and addiction in diverse populations, with a focus on sustainable and scalable interventions that can be rapidly implemented by healthcare systems.

In addition, recent discoveries in human genetics and molecular biology will be incorporated into the development of a novel team-based platform to rapidly test targets and candidate therapeutics for diverse human pain conditions and share findings with the wider pain research community. This research will address pain systems and allow for a variety of research questions including conditions of chronic analgesic use, other drug use, substance use disorders (SUDs) and other co-morbid conditions, and will enable and accelerate human gene- and cell- based validation of pain therapeutic targets through the HEAL initiative and other pipelines. This will build on existing HEAL research on preclinical and translational research in pain, and ongoing efforts to accelerate the development of novel treatments for pain. Through these and other efforts at HEAL and across the NIH, we aim to continue to improve our understanding of pain and develop non-addictive, effective therapies.

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. Overall, 6 million Americans living with migraines are active opioid users. I strongly support the NIH Heal Initiative to find solutions to curb the national opioid public health crisis by understanding, managing, and treating pain. While migraine grant proposals are eligible for consideration under the HEAL request for applications (RFAs) issued for pain research, less than 1 percent of HEAL Initiative appropriations have funded headache disorders research—the least funded NIH area among all the nation's burdensome diseases. I am very concerned about the failure 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 Back Pain Consortium (BACPAC) group of RFAs for research on back pain?

Answer. The National Institutes of Health (NIH) recognizes the burden of pain at the individual and population levels and that headache disorders are prevalent and disabling conditions which affect millions of Americans. The NIH launched the HEAL Initiative (Helping to End Addiction Long-term) to improve pain care and better prevent and treat opioid use disorder. Priorities of the HEAL initiative, developed with our stakeholders with expertise in pain research and care, include enhanced understanding of pain, discovery and validation of novel pain therapeutic targets, testing therapies in clinical settings, and accelerating the process to bring new therapies to patients. The initiatives are, or were, open to all pain conditions. The HEAL initiative also established much needed research infrastructure to sup-

[39] www.iprcc.nih.gov/federal-pain-research-strategy-overview.

port innovative science. Headache research fits within the scope of all these initiatives and will benefit from the enhanced infrastructure.

HEAL funding solicitations call for proposals across all pain conditions. NIH staff recognizes the low submission rate of headache applications and broadly disseminates information on HEAL and other funding announcements to the research community to encourage submissions. Most funding announcements specifically cite headache as an area of interest and others are inclusive of headache. Low back pain is an exception among pain conditions in that it has unique research gaps such as lack of diagnostic tools and technologies, no accepted common data elements, poor diagnostic criteria, complex etiology, and lack of an adequate evidence base for effective practice guidelines. The HEAL Back Pain Consortium (BACPAC) initiative was launched to fill these extensive gaps to improve pain care across the spectrum of low back pain.

Migraine and other headache disorders have good classification schemas, a range of effective treatment therapies whose development was supported by NIH research, and evidence-based diagnostic categories and treatment protocols (International Headache Society). Our understanding of migraine etiology is more advanced than that for back pain. NIH has supported transformative basic research that advanced our knowledge of migraine mechanisms, causes, and predictors, biomarker identification, and new therapy development. For example, NIH supported investigators provided the foundation for development of CGRP antibodies now used widely for migraine therapy. NIH sponsored research also contributed to understanding how migraine auras activate nociceptors and initiate a migraine, and the mechanism of action for new migraine therapies such as vagus nerve stimulation. Basic research on potassium channels, delta, or kappa opioid receptors, and TRP channels fundamentally increased our understanding of trigeminal nociceptors and their involvement in initiating a migraine, giving us new targets for potential treatments. An NIH sponsored pivotal pediatric migraine clinical trial changed clinical practice for children with chronic daily headaches.

NIH and HEAL leadership recognize that far too many headache sufferers are prescribed opioids despite clear clinical practice guidelines that call for non-opioid effective alternatives rather than opioids. This practice reflects the sparsity of headache specialists and the lack of and education of our primary care providers who are often the first to treat those with disabling migraines. NIH also recognizes the need to expand the headache research workforce. The HEAL initiative recently released funding announcements to support training and mentorship of early and mid-career researchers in the field of basic, translational, and clinical pain research. We encourage those interested in headache research to benefit from these opportunities.

QUESTIONS SUBMITTED TO DR. ANTHONY FAUCI

QUESTIONS SUBMITTED BY SENATOR RICHARD J. DURBIN

Question. I have received a lot of questions from Illinois families, who are hoping for more clarity on the CDC's most recent mask guidelines. Many vaccinated parents—with unvaccinated children at home—are wondering if they should be wearing masks when out in public.

What advice would you give to vaccinated parents who have unvaccinated children at home?

When do you think we will have a COVID vaccine approved for children younger than 12 years of age?

Answer. Currently authorized coronavirus disease 2019 (COVID–19) vaccines meet the U.S. Food and Drug Administration's (FDA's) rigorous standards for safety and effectiveness, and current data suggest that fully vaccinated people are less likely to transmit severe acute respiratory syndrome coronavirus 2 (SARS–CoV–2) to others. According to the Centers for Disease Control and Prevention (CDC), fully vaccinated people—including those living with unvaccinated children or adolescents—can resume activities without wearing masks or physically distancing, except where required by Federal, state, local, tribal, or territorial laws, rules, and regulations. Individuals ages 2 and older who are unvaccinated, however, should continue to wear masks in public and when around people who do not live in their household, except when eating or sleeping. CDC will continue to evaluate and update public health recommendations for fully vaccinated people as more information, including on Delta and other new variants, becomes available.

Efforts to evaluate COVID–19 vaccines in children under age 12 currently are underway, and a COVID–19 vaccine may be available for this age group by the end of 2021. On March 16, 2021, Moderna, in collaboration with the National Institute

of Allergy and Infectious Diseases (NIAID) and the Biomedical Advanced Research and Development Authority (BARDA), launched KidCOVE, a Phase 2/3 study to evaluate the safety and efficacy of the Moderna COVID–19 vaccine in children ages 6 months to less than 12 years. Pfizer also is conducting a Phase 1/2/3 trial to evaluate its COVID–19 vaccine in this age group. In addition, other vaccine developers are planning to begin trials to test their vaccine candidates in children. Until a COVID–19 vaccine is available for children under age 12, it will be important for all individuals, especially children and other unvaccinated individuals, to continue to follow all public health measures for COVID–19 advised by the CDC, including frequent hand washing and the use of masks and social distancing in certain settings.

QUESTIONS SUBMITTED BY SENATOR JOE MANCHIN, III

Question. My home state of West Virginia is battling an epidemic during the middle of a pandemic. My state has been devastated by the drug epidemic, COVID–19, and we now lead the nation in new HIV infection rates. You have spent much of your career focused on the prevention, diagnosis, and treatment of HIV/AIDS. Your research has been instrumental in saving countless lives in the United States and around the world. The National Institute of Allergy and Infectious Diseases supports initiatives focused on diagnosing, treating, preventing and responding to the HIV epidemic in the United States. These efforts represent steps in the right direction, but will not alone end West Virginia's increasing numbers of new HIV infections and other opioid-related infectious diseases.

What is being done to replicate testing and surveillance efforts we saw put into place for COVID–19 for other infectious diseases, like HIV/AIDS?

What public health infrastructure would be required to bring better infectious disease testing and surveillance to fruition?

Answer. The Federal response to coronavirus disease 2019 (COVID–19) relied heavily on the utilization and expansion of existing resources for human immunodeficiency virus (HIV) and other infectious diseases. By leveraging available resources, we have been able to accelerate the development of diagnostic tests and other medical countermeasures, as well as surveillance and community engagement efforts. In turn, knowledge gained from the COVID–19 response may inform strategies to address other infectious diseases such as HIV. This includes efforts undertaken by the U.S. Department of Health and Human Services (HHS) to end HIV in the United States by 2030 through the Ending the HIV Epidemic in the U.S. (EHE) initiative. EHE is coordinating across HHS agencies and with patient, community, academic, and other partners to plan, design, and deliver local HIV prevention and care services. This "whole-of-society" approach is a model for ending both the HIV epidemic as well as the COVID–19 pandemic. Proper diagnosis and treatment of HIV are key components of this initiative, and efforts to improve testing and surveillance for HIV are ongoing.

An important aspect of the response to the COVID–19 pandemic as well as the HIV epidemic is community engagement. The National Institute of Allergy and Infectious Diseases (NIAID), in cooperation with the Department of Defense, established the COVID–19 Prevention Network (CoVPN) by leveraging existing NIAID-funded clinical trials networks, including networks focused on HIV treatment and prevention. The CoVPN built on existing community relationships to enhance trust and meaningful engagement in key racial and ethnic minority communities throughout the United States to promote diverse participation in clinical trials for COVID–19. The community relationships enhanced by the CoVPN may be further leveraged to advance efforts, including testing and surveillance, for HIV and other infectious diseases.

The National Institutes of Health (NIH) also anticipates that the rapid establishment of COVID–19 testing and surveillance may help to address HIV and other infectious diseases. NIH launched the Rapid Acceleration of Diagnostics (RADx) initiative to speed innovation in technologies to test for severe acute respiratory syndrome coronavirus 2 (SARS–CoV–2), in partnership with the Biomedical Advanced Research and Development Agency (BARDA), the Centers for Disease Control and Prevention (CDC), the U.S. Food and Drug Administration (FDA), and the Defense Advanced Research Projects Agency (DARPA). As part of RADx, NIH and CDC are evaluating whether frequent self-administered, at-home SARS–CoV–2 testing helps reduce community transmission of SARS–CoV–2. Efforts to develop and deploy rapid, point-of- need diagnostics for SARS–CoV–2—including at-home testing kits—may inform community-based testing and surveillance strategies for other infectious diseases, including HIV.

NIH and NIAID will continue to build on investments in improved diagnostic tests for SARS- CoV–2 to support the development of novel diagnostic tests for other infectious diseases such as HIV. In addition, lessons learned on the best way to integrate and expand on existing research efforts and infrastructure will be invaluable as we continue to prepare for—and respond to— other existing and emerging infectious disease threats.

As discussed in response to part a of this question, the Federal response to the COVID–19 pandemic has strengthened existing partnerships and coordination mechanisms, as well as established new partnerships that will inform the response to future infectious disease pandemics and existing epidemics, such as the HIV/AIDS epidemic in the United States. The coordinated efforts through RADx and the CoVPN allowed us to leverage the intrinsic strengths from public and private sector partners to achieve an unprecedented level of scientific achievement and community engagement. When the COVID–19 pandemic ends, lessons learned from our experiences with RADx and the CoVPN will continue to help inform efforts to address other infectious disease threats.

NIH and NIAID will continue to work with HHS Operating Divisions and other Federal agencies to identify the actions that were most effective in responding to the COVID–19 pandemic. This information may result in new initiatives, strategic plans, and/or formal assessments of pandemic preparedness.

QUESTIONS SUBMITTED BY SENATOR RICHARD C. SHELBY

Question. As America begins to assist the world to vaccinate all who want it, the current vaccine options can be problematic for countries without the infrastructure to store vials in a cooled or frozen environment.

How beneficial could an effective, intranasal vaccine option be for developing countries that cannot store the current vaccines at frigid temperatures or produce the healthcare workers to give the shot?

Do you see this option benefitting Americans who may be hesitant to receive the current vaccine dosage in a shot?

Answer. Global access to safe, effective vaccines will be critical to address the coronavirus disease 2019 (COVID–19) pandemic. Limiting the spread of the severe acute respiratory syndrome coronavirus 2 (SARS–CoV–2) virus in foreign countries helps to control the pandemic in those countries while also limiting the development and spread of variants that could eventually be introduced into the United States. To enhance vaccine availability in foreign countries, the Biden Administration has supported and contributed to COVAX, a global mechanism for equitable access to COVID–19 vaccines. COVAX has delivered COVID–19 vaccines to more than 100 countries, the majority of which have lower-income economies. The United States also has made millions of doses of COVID–19 vaccines available to other countries to support vaccination campaigns around the world.

Existing COVID–19 vaccines are being successfully administered globally, and several COVID–19 vaccines authorized for emergency use or in clinical testing in the United States can be shipped and stored at refrigerator temperatures (2–8 degrees Celsius). Still, the development of vaccines that can be administered with less skill and/or stored at warmer temperatures have the potential to expand vaccination efforts both in the United States and abroad. The National Institute of Allergy and Infectious Diseases (NIAID) is supporting the development of vaccine candidates and platforms that may be more accessible and convenient than currently available COVID–19 vaccines, including a single-dose intranasal SARS–CoV–2 vaccine candidate called ChAd-SARS–CoV–2–S. NIAID scientists and collaborators recently showed that the intranasal ChAd–SARS–CoV–2–S vaccine candidate limited infection in non-human primates. Novel vaccines with alternative administration strategies, such as intranasal vaccines, may reduce barriers to transporting and administering vaccines in developing countries. It is important to note, however, that these vaccines may still need to be kept at low temperatures or may require administration by a healthcare provider with specialized training to ensure accurate dosing and administration. For example, FluMist Quadrivalent—a U.S. Food and Drug Administration-approved intranasal vaccine against influenza—must be administered by a healthcare provider in the United States.

In addition, National Institutes of Health (NIH) scientists and NIH-supported researchers are studying additional vaccine delivery technologies, including vaccines that can be orally administered or that utilize microneedles in patches placed on the skin to deliver the vaccine. For example, NIH scientists have begun preclinical evaluation of a virus-like-particle-based vaccine candidate for SARS–CoV–2 that can be administered orally, and NIH-supported researchers are evaluating a patch-based

vaccine for SARS–CoV–2. An NIH-supported Phase I trial of a patch-based vaccine candidate for influenza showed that individuals that received the vaccine had a similar immune response to those receiving the influenza vaccine via intramuscular injection. NIH also is supporting the development of another promising patch-based vaccine candidate for influenza that uses biodegradable microneedles originally developed through NIH-supported research to stabilize vaccines and antibiotics outside of the cold chain. Although additional testing will be necessary, orally administered and patch-based vaccines may prove to be an invaluable tool in resource-limited settings as they may require little to no refrigeration, as well as less training to administer correctly.

As we work to address the COVID–19 pandemic, as well as other infectious disease threats, recent innovations in vaccine technology will help make it easier to get vaccines to areas that can be difficult to serve with traditional vaccines. NIH continues to support research on intranasal, oral, and patch-based vaccine platforms, all of which could be highly adaptable for use against a number of infectious pathogens.

Vaccines that can be administered intranasally may be considered less invasive than those that require an injection. Such an option may encourage individuals who are hesitant to receive the COVID–19 vaccines currently authorized for emergency use in the United States, which are all administered via intramuscular injection, to become vaccinated. Additional vaccine delivery technologies, such as oral or patch-based vaccines may also provide additional flexibilities when trying to reach individuals in resource-limited areas or who are vaccine hesitant or needle adverse. As noted in the response to part a of this question, NIAID is supporting and will continue to support the development of vaccine candidates with different delivery technologies to reduce vaccine hesitancy as well as barriers to vaccine access.

QUESTIONS SUBMITTED TO DR. DIANA BIANCHI AND DR. ELISEO PÉREZ-STABLE

QUESTIONS SUBMITTED BY SENATOR RICHARD J. DURBIN

Question. Our nation continues to struggle with racial disparities, especially in maternal health. The U.S. is one of only 13 countries where our nation's maternal mortality rates are worse now than they were 25 years ago. Every year, 700 women in the U.S. die as a result of their pregnancy—and more than 60 percent of these deaths are preventable. Tragically, African American and Hispanic women are three times as likely as White women to die from pregnancy-related issues. For years, I have introduced the MOMMA's Act with Rep. Robin Kelly, and I'm so pleased that a major component of our bill was recently signed into law as part of the American Rescue Plan. Now states can follow in Illinois' footsteps by allowing new moms to keep their Medicaid coverage for a full year, versus just 60 days.

What research NIH is doing in this space?

How is NIH working to actually improve maternal and infant healthcare?

Answer. Maternal health is a priority for the National Institutes of Health (NIH) and multiple NIH institutes have heavily invested in research to prevent maternal morbidity and mortality (MMM) and improve health for women, before, during, and after pregnancy. In fiscal year 2020 NIH supported $407 million in research on maternal health and $224 million in research on MMM.

In a year that was dominated by both the coronavirus disease 2019 (COVID–19) pandemic and renewed calls to combat health disparities and inequities, NIH ensured these challenges were integrated into efforts to reduce MMM. In March 2020, researchers in the Eunice Kennedy Shriver National Institute of Child Health and Human Development's (NICHD) Maternal-Fetal Medicine Units Network designed the Gestational Research Assessments for COVID–19 (GRAVID) study, which evaluated data from more than 1,200 pregnant women at 33 hospitals across the country and found that pregnant COVID–19 patients with severe disease are at higher risk for cesarean delivery, postpartum hemorrhage, hypertensive disorders of pregnancy, and preterm birth. Data from the study is being shared with a larger registry to inform future studies of COVID–19's effects on pregnancy and maternal health.

Tackling the challenge of reducing maternal MMM requires strong partnerships with and among local communities and resources, particularly with racial and ethnic minority populations that experience stark health disparities. To that end, several NIH Institutes, Centers, and Offices (ICOs) held community engagement activities to hear first-hand how patient communities can inform future research and what engagement strategies might enhance local efforts to improve maternal health. A common refrain was that research conducted in a community should be developed with and vetted by the community to ensure success and improved outcomes. These

engagement activities informed the development of the IMPROVE (Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone) Initiative, which aims to build an evidence base that will improve maternal care and outcomes from pregnancy through 1 year postpartum. IMPROVE is co-led by NICHD and the NIH Office of Research on Women's Health and engages over 30 ICOs to research the leading causes of maternal mortality in the United States—cardiovascular disease, infection, and immunity—as well as contributing health conditions or social factors, such as mental health disorders, diabetes, obesity, substance use disorders, and structural and healthcare system issues that disproportionately affect Black pregnant and postpartum women. IMPROVE prioritizes comprehensive, interdisciplinary research that engages communities with high rates of maternal deaths and complications. This work will help create tailored, evidence-based solutions for pregnant and postpartum women.

NIH research on MMM generates evidence that improves outcomes and clinical care, and several NIH Institutes have strong investments in this space. For example, an NICHD-funded study demonstrated that when hospitals implemented evidence-based recommendations for clinical practice there was a reduction in the risk of severe maternal morbidity from obstetric hemorrhage, a common complication of childbirth. The reduction was more dramatic for Black women more than for White women, reducing disparities and improving outcomes. NICHD is also supporting a machine learning framework to predict severe maternal morbidity. Researchers aim to analyze population-based data from Maryland state databases and hospital surveys to develop techniques that can predict maternal risks early. Identifying key predictors of severe maternal morbidity can help ascertain health disparities, strengths and weaknesses in obstetric care, and prevent adverse maternal and neonatal outcomes.

In fiscal year 2020, the National Institute on Minority Health and Health Disparities (NIMHD) started an initiative entitled Addressing Racial Disparities in Maternal Mortality. This initiative supports multidisciplinary research projects that examine the clinical, social, behavioral, and healthcare system interventions to address racial disparities in MMM in the United States. Additionally, NIMHD funded the Maternal and Developmental Risks from Environmental and Social Stressors (MADRES) project in collaboration with the National Institute on Environmental Health Sciences, to examine prenatal environmental exposures and social stressors in relation to depression and cardiovascular risk factors postpartum.

The National Heart, Lung, and Blood Institute (NHLBI) is weaving together a network of community-engaged researchers who will not only work to improve women's heart health and reduce maternal mortality, but will also address other health disparities. For example, NHLBI's new Maternal Health Community Implementation Program, will fund three or four regional coalitions to pilot test community-based strategies in areas where maternal death rates are high, particularly in the southeast. Additionally, NHLBI's Early Intervention to Promote Cardiovascular Health of Mothers and Children (ENRICH) will tap into existing Federal home health/wellness programs that serve at-risk families to determine if adding a cardiovascular intervention will enhance maternal and early childhood outcomes. Approximately 3,000 mother- child pairs across various sites will be reached as part of this effort.

These are just a few examples of how NIH's broad investment in addressing MMM is improving maternal and infant care.

QUESTIONS SUBMITTED BY SENATOR JEANNE SHAHEEN

Question. I am hopeful that our continued investment in the Special Diabetes Program, and diabetes research at NIH as a whole, can help spur a new wave of breakthroughs, and maybe one day a cure for diabetes.

Now that Congress has secured longer-term funding for the Special Diabetes Program, can you please provide information on NIH's priority areas for Special Diabetes Program research in the years to come?

Answer. The National Institutes of Health (NIH) appreciates the recent extension of the Special Diabetes Program, which will allow us to continue critical ongoing research programs and to support new research to improve the health and quality of life of people with or at risk for type 1 diabetes and its complications. For example, the recent extension will allow the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to continue the Human Islet Research Network, which is working to better understand how insulin-producing cells are lost in type 1 diabetes and to find strategies to replace or protect them in people, toward curing the disease. NIDDK plans to begin new clinical trials through the Type 1 Diabetes

TrialNet network, testing agents to prevent onset of clinical type 1 diabetes. Such research will build on the landmark success of previous TrialNet research demonstrating for the first time ever that early preventive treatment can delay onset of clinical type 1 diabetes in high-risk individuals. NIDDK also plans to support research building on the tremendous recent progress in developing transformative diabetes management technologies, such as artificial pancreas devices. For example, future research is needed to improve components of artificial pancreas devices (e.g., glucose sensors, hormone formulations), develop simpler and more user-friendly devices, and test devices in understudied populations (e.g., older adults, pregnant women, people with poorly controlled blood glucose levels). This type of research will move us closer to our goal of developing multiple different artificial pancreas technologies for people of all ages so that they can choose the technology best suited to their clinical needs. NIDDK also plans to support new research to identify novel ways to detect and monitor type 1 diabetes onset and progression, such as by determining whether "extracellular vesicles" that originate from pancreatic tissue may be useful to detect earlier stages of type 1 diabetes than currently possible. NIDDK is collaborating with the National Heart, Lung, and Blood Institute on new research toward reducing cardiovascular disease in people with type 1 diabetes, as very little is known about how best to prevent and treat this life-threatening complication. To inform other future research directions, NIDDK is spearheading a planning meeting in spring 2022 under the auspices of the statutory Diabetes Mellitus Interagency Coordinating Committee to obtain input from external scientific and lay experts on critical new and emerging research opportunities that could be supported by the Special Diabetes Program.

Question. New Hampshire continues to be one of the hardest-hit states in the substance use disorder epidemic, with one of the highest overdose death rates in the country. I am very supportive of the ongoing work at the National Institute on Drug Abuse (NIDA) to research potential non-addictive alternatives to opioids for pain management.

Could you discuss progress on any research within NIDA to study these types of alternatives?

Answer. The National Institutes of Health (NIH) recognizes the need to improve pain management without risk of addiction and other serious side effects. NIH is taking a multi-pronged approach to develop safe and effective therapies to reduce our reliance on opioids.

To avoid replay of the spike in opioid deaths related to over-use of medical opioids for pain management we need more effective, non-addictive pain medications and data that can inform best practices in pain care. The NIH Helping to End Addiction Long-term (HEAL) Initiative was launched in 2018 and significantly expanded research to discover and accelerate development of non-addictive pharmacological and non-pharmacological pain treatments. HEAL has awarded over $1.5 billion for research to improve pain management and address opioid use disorder and overdose. Studies supported by HEAL, the Blueprint Neurotherapeutics Program, and multiple NIH Institutes, in particular the National Institute for Neurological Disorders and Stroke (NINDS), are underway to identify, optimize and test promising molecules, biologics, and devices that target non-opioid pain pathways in the nervous system. Biomarker studies to help with diagnosis of pain conditions and to identify patients most likely to respond to a particular treatment will enhance pain clinical trials and improve best practices are moving forward. In addition, non-pharmacological approaches to manage many different pain conditions are being evaluated through effectiveness and implementation research approaches.

The NIH HEAL initiative established essential pain research infrastructure to accelerate development of new medications and devices to treat pain. An analgesic screening platform uses animal- and human cell-based models such as neural tissue chips for rapid screening of molecules or devices for analgesic relevant biological and pain behavioral activity. HEAL, with input from academic and industry partners, established an Early Phase Pain Investigation Clinical research network (phase 2 studies) to test safety and efficacy of novel therapeutics and a later stage pain management Effectiveness Research Network (ERN) to compare effectiveness of pharmacological and non-pharmacological approaches in many different pain conditions. The ERN is supporting eight large trials for various pain management strategies. The Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid Prescribing (PRISM) network focuses on clinical trials of non-pharmacologic pain therapies in healthcare systems.

The Phase 2 network will launch trials on two new analgesics in 2021. The ERN is supporting eight large trials for various pain management strategies. PRISM is supporting six large trials in healthcare systems. In addition, HEAL established an analgesic development pipeline to accelerate the development and testing of novel

drugs and devices. This program uses team-based science coupled with a comprehensive set of research resources to bring new therapeutics rapidly to the clinic. To advance the discovery and validation of new drug targets, HEAL has funded over 30 projects to discover and verify a diverse set of drug target types across multiple pain conditions, six drug optimization studies on new safe and effective pain treatments, and 11 projects to test the effectiveness of implanted devices and noninvasive stimulation of nerves in the brain or throughout the body to reduce perception of pain. This effort greatly expands on NINDS supported studies in these areas.

Recent HEAL accomplishments toward new therapeutics include two patent filings for small molecule modulators of pain receptors involved in chronic pain and migraine. One ongoing study received Investigational New Drug (IND) approval for use of buprenorphine with nonpharmacological treatment to relieve pain in patients undergoing kidney dialysis. Through the NIH Blueprint Neurotherapeutics Program researchers are developing non-addictive kappa opioid receptor antagonists for treatment of migraine and a safe, non-opioid epoxide hydrolase inhibitor to reduce diabetic nerve pain. Earlier, NIH supported basic science research led to calcitonin gene-related peptide therapy for migraine and nerve growth factor therapy for inflammatory pain. Drugs that target these molecules are now approved by the U.S. Food and Drug Administration to treat migraine and osteoarthritis pain. Through the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, which is a major effort to develop tools to map, monitor, and modulate neural circuits, NIH has supported studies that will enhance diagnostics and therapies for chronic pain and other neural circuit disorders.

Question. The Institutional Development Award (IDeA) program at NIH has proven critical in funding New Hampshire researchers, including especially the innovative work at Dartmouth College and Dartmouth-Hitchcock Health. I am hopeful that Congress can continue to support funding for this program.

Can you provide any insight into how NIH is currently making use of Institutional Development Award funds and whether more funding for the program would be helpful?

Answer. The Institutional Development Award (IDeA) supports basic, clinical, and translational research, faculty development, and infrastructure improvements at institutions in states and territories that have historically received a lower aggregate level of NIH funding. The program aims to strengthen biomedical research capacity, enhance the competitiveness of investigators in securing research funding, and enable clinical and translational research that addresses the specific needs of rural and medically underserved communities. Currently, institutions in 23 States and Puerto Rico are eligible for funding through the IDeA Program, the various components of which include:

—*IDeA Networks of Biomedical Research Excellence (INBRE).* INBRE enhances, extends, and strengthens the research capabilities of biomedical research faculty in IDeA states through a statewide program that links a research-intensive institution with primarily undergraduate institutions. INBRE supports institutional research and infrastructure development; research by faculty, postdoctoral scientists, and students at participating institutions; and targeted outreach to build science and technology knowledge within a state's workforce. Only one INBRE award is made per IDeA-eligible state. The New Hampshire INBRE, which is led by Dartmouth and co-led by the University of New Hampshire, is in its twelfth year of operation and has used the program's support to improve and expand research capacity at all eight of its partner institutions, including adding additional labs, cores and instrumentation/infrastructure; establishing fully functional Office of Sponsored Programs for faculty members to competitively seek extramural grants; training and mentoring of both faculty and students; and enhancing a vibrant institutional research culture. In fiscal year 2020, the National Institute of General Medical Sciences (NIGMS) supported 24 INBRE awards.

—*Centers of Biomedical Research Excellence (COBRE—Phases I, II, and III).* COBRE supports the establishment and development of innovative, state-of-the-art biomedical and behavioral research centers at institutions in IDeA-eligible states that: (a) galvanize multidisciplinary research to develop a critical mass of investigators that are competitive for peer-reviewed research funding; (b) provide improvements to research infrastructure; and (c) maintain research cores to sustain a collaborative, multidisciplinary research environment that includes pilot project programs, mentoring, and workforce training. In fiscal year 2020, NIGMS supported 112 COBRE awards. One such example, a Phase I COBRE at Dartmouth's Geisel School of Medicine called iTarget (Institute for Biomolecular Targeting), aims to catalyze the development of new therapeutic approaches to address cancer, chronic obstructive pulmonary disease, and res-

piratory syncytial virus, a common viral infection that can be dangerous to young children and the elderly. This COBRE is providing unique resources to investigators at Dartmouth and its IDeA partners, thus enhancing research productivity and funding competitiveness across the region.

—*IDeA Networks for Clinical and Translational Research (IDeA–CTR).* IDeA–CTRs develop a network infrastructure and capacity in IDeA-eligible states to conduct clinical and translational research focused on health concerns that disproportionately affect rural and medically underserved populations and/or that are prevalent in IDeA states. IDeA–CTR awards support mentoring and career development activities in clinical and translational research. In fiscal year 2020, NIGMS supported 12 IDeA–CTR awards.

—*Regional Technology Transfer Accelerator Hubs.* NIGMS established the Regional Technology Transfer Accelerator Hubs for IDeA states in each of the four IDeA regions (central, northeast, southeast, and western regions). The hubs provide both consulting services and skills development in entrepreneurship, technology transfer, small business finance, and other areas needed to transform important discoveries made in the laboratory into potentially viable commercial products that address human health. In fiscal year 2020, NIGMS supported four accelerator hubs. The northeast hub is located at Celdara Medical in Lebanon, New Hampshire.

—*Research Co-Funding.* NIGMS provides co-funding for applications from IDeA state institutions that have been judged meritorious by NIH peer-review committees and national advisory councils but that may also fall outside the usual range of support by a given NIH Institute or Center (IC). In fiscal year 2020, NIGMS co-funded 42 research project grants at 20 NIH ICs; one of these was at Dartmouth College.

QUESTIONS SUBMITTED TO DR. NED SHARPLESS

QUESTIONS SUBMITTED BY SENATOR PATTY MURRAY

Question. The American Cancer Society's Annual Report to the Nation on the Status of Cancer highlighted that we are making good progress in the battle against cancer, with the incidence and mortality rates for most cancers have dropped significantly. However, among the 20 most common cancers, relative survival for patients significantly improved since the mid-1970s except for those with uterine cancer.

What plans does the NCI have in fiscal year 2022 to develop a paradigm of increased research to improve hope for survival for patients with uterine cancer?

Answer. The National Cancer Institute (NCI) shares the committee's commitment to research on uterine cancers, including endometrial cancer (cancer of the inner lining of the uterus), and improving outcomes for patients.

Today, nearly 40 percent of adults are obese, and without intervention, the obesity epidemic will result in more cancers. Uterine cancer incidence and mortality have increased in recent years,[40] believed to be partially associated with rising rates of obesity.[41] Women who are obese or overweight are approximately two to four times as likely as normal weight women to develop uterine cancer, including endometrial cancer, making interventions to address weight and obesity vital to combatting uterine cancer incidence and mortality. Examples of NCI-supported research on this topic include a study of how changes in body composition following weight loss impact inflammatory biomarkers in biopsy-collected endometrial tissue and blood samples and whether these processes differ between Black and White women;[42] the development of a weight loss intervention among Appalachian residents;[43] and a study of the Deep South Interactive Voice Response (IVR)-supported Active Lifestyle (DIAL) Intervention to increase physical activity levels among residents of the Deep South.[44]

Researchers at the University of North Carolina Lineberger Comprehensive Cancer Center are directly examining the metabolic and molecular differences of endometrial tumors in obese and non-obese women. In addition, this research team is exploring how metformin, widely used to treat type II diabetes, may also exhibit anti-tumor activity through its effects on a patient's metabolism.[45]

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[40] pubmed.ncbi.nlm.nih.gov/30521505/,seer.cancer.gov/report__to__nation/statistics.html#factors.

[41] www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet.

[42] reporter.nih.gov/project-details/10129305.

[43] reporter.nih.gov/project-details/10065366.

[44] reporter.nih.gov/project-details/10163139.

[45] reporter.nih.gov/project-details/10104456.

Translational research to bridge the gap between basic research on endometrial cancer and potential therapies is also essential to improving outcomes for patients. NCI supports a Specialized Program of Research Excellence (SPORE) focused on translational research for endometrial cancer at the University of Texas/MD Anderson Cancer Center. This SPORE is conducting research aimed at developing therapeutic strategies for advanced/recurrent endometrial cancer and aggressive subtypes, addressing unmet clinical needs in prevention and conservative therapy of high-risk precancerous lesions and low-grade endometrial cancer, and incorporating molecular diagnostics into clinical decisionmaking.[46]

As of July 2021, NCI is supporting over 150 clinical trials with a primary focus on uterine (including endometrial) cancer. Examples of these projects include studies of the use of an immunotherapy agent, in combination with other cancer therapies, to treat high risk endometrial cancer;[47,48] a trial examining a combination therapy to treat endometrial cancers that express the HER2 protein;[49] and a study evaluating the use of the experimental therapy triapine to treat endometrial serous adenocarcinoma, a difficult to treat subtype of uterine cancer.[50] Clinical trials are an integral part of advancing research in this important topic area, and NCI is committed to reaching out to disparate, at-risk communities to explain, educate, and encourage clinical trial participation.

As part of the National Institutes of Health (NIH) efforts to identify future research directions, NCI and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) explored research opportunities into the progression of benign gynecologic conditions to cancers through a collaborative workshop in April 2019. Currently, NICHD funds research on benign gynecologic conditions such as endometriosis and uterine fibroids, while NCI funds research on women's cancers. The workshop sought to bridge the two research areas and identify gaps in the biologic, epidemiologic, and clinical understanding of progression from benign conditions to cancer. The workshop addressed three gynecologic disease types: (1) endometriosis or endometrial cancer and endometrial-associated ovarian cancer, (2) uterine fibroids (leiomyoma) or leiomyosarcoma, and (3) denomyosis or adenocarcinoma. Working groups were formed for each disease type, and key questions and current challenges that emerged from the discussions, along with potential research opportunities to advance understanding of progression of gynecologic benign conditions to cancer, were published. Specific research questions and gaps were identified in all three focus areas, and several cross-cutting topics emerged. The results of this workshop, as well as ongoing horizon- scanning activities, will continue to inform NIH's next steps to address uterine cancer.

Question. Non-Hispanic Black women are two time as likely as non-Hispanic White women to die from uterine or cervical cancer (https://www.ajog.org/article/S0002-9378(16)46212- 5/pdf).

Can NIH/NCI please share with the Committee the research activities the NCI is supporting to address this disparity, particularly with regards to access to care, prevention, early diagnosis, treatment completion and developmental therapeutics?

Answer. The National Cancer Institute (NCI) shares the Committee's concern regarding cervical and uterine/endometrial cancer disparities and is working to support research to eliminate these disparities, as well as cancer disparities more broadly. Examples of research aimed at addressing disparities in uterine and cervical cancer outcomes are provided below.

NCI is a leader in developing and supporting definitive, practice-changing gynecologic (GYN) clinical trials, as well as responding to areas of scientific inquiry that are unaddressed by private industry. The NCI GYN Cancers Steering Committee sets clinical trials strategic priorities that address areas of unmet clinical need, important unanswered clinical questions, and potential new approaches to disease treatment.[51] The Institute has supported and advanced GYN cancer research that will provide greater insight into these cancers, additional options for drug therapies, and improved surgical techniques with the intent of increasing survivorship and quality of life. As of July 2021, NCI is supporting over 150 interventional clinical trials with a primary focus on uterine (including endometrial) cancer, two trials on the rare uterine sarcoma, and nearly 100 trials for cervical cancer patients. NCI also has several trials that are "disease agnostic," meaning that they are open to patients with certain genetic alterations rather than traditional cancer types, cre-

[46] trp.cancer.gov/spores/endometrial.htm.
[47] clinicaltrials.gov/ct2/show/NCT04214067.
[48] clinicaltrials.gov/ct2/show/NCT03914612.
[49] clinicaltrials.gov/ct2/show/NCT04585958.
[50] clinicaltrials.gov/ct2/show/NCT04494113.
[51] www.cancer.gov/about-nci/organization/ccct/steering-committees/nctn/gynecologic.

ating opportunities for patients to potentially benefit from precision medicine and targeted therapy.

A recent study led by NCI intramural researchers used population data from NCI's Surveillance, Epidemiology, and End Results (SEER) database to evaluate trends of hysterectomy-corrected uterine cancer incidence rates for women overall and by race and ethnicity, geographic region, and histologic subtype. Correct estimation of these rates requires accounting for hysterectomy prevalence, which varies by race, ethnicity, and region. The researchers found that incidence rates of common subtypes of uterine cancer were stable in non-Hispanic White women over the study period and increased in women of other racial/ethnic groups. By contrast, incidence rates of aggressive subtypes have been increasing dramatically over time in all racial/ethnic groups; in particular, much higher rates of these aggressive subtypes were observed in Black women than in other racial/ethnic groups. The researchers also observed that survival rates were lower among all women with aggressive subtypes than among women with common subtypes, and Black women had the lowest survival rates within each stage at diagnosis or histologic subtype.

Uterine serous carcinoma (USC) is a rare but aggressive type of endometrial cancer. In about one-third of women with USC, their tumor cells overproduce a protein called HER2 (human epidermal growth factor receptor 2), which is associated with poor prognosis in women with endometrial cancer. Black women with endometrial cancer are more likely than White women to be diagnosed with UCS and are more likely than women of other races/ethnicities to have HER2 overproducing UCS tumors. NCI clinical studies for patients with HER2 overproducing uterine serous cancer and carcinosarcoma are currently in development.

NCI-supported researchers are working to describe additional differences in subtypes of uterine and endometrial cancers, with the eventual goal of targeting therapies to treat each disease subtype. For example, investigators at Brigham and Women's Hospital, using data from the NCI-supported Epidemiology of Endometrial Cancer Consortium (E2C2),[52] are studying genomic variation across the full spectrum of endometrial tumors, distinct risk factor profiles across tumor types, and the role of underlying tumor biology to better understand the disparities in outcomes between African-American and non-African-American women.[53] NCI-supported investigators at Wayne State University are examining aggressive subtypes of high-grade endometrial tumors, including endometrioid, serous, clear cell and mixed carcinomas, by analyzing both clinical and genetic data in 500 women (250 African-American, 250 White) diagnosed with these cancers.[54] In addition, NCI is supporting a planning grant to establish a Specialized Program of Research Excellence (SPORE) at Northwestern University focused on gynecologic cancer disparities. One of the pilot projects will focus on the tumor genomics of endometrial cancer.[55]

To more accurately evaluate the risk of cervical precancer and study novel biomarkers in women undergoing cervical cancer screening, intramural researchers in NCI's Division of Cancer Epidemiology and Genetics have partnered with the University of Mississippi Medical Center and the Mississippi State Department of Health in the STRIDES Study (Studying Risks to Improve Disparities of cervical cancer in Mississippi). This study, based in one of the top five states for cervical cancer incidence and mortality, combines the expertise of clinicians, laboratory scientists, epidemiologists, and implementation scientists to address all aspects of cervical cancer prevention and control.[56]

In 2020, NCI launched the "Last Mile Initiative," with the goal of improving cervical cancer screening coverage to underserved, never screened, and under-screened women. This initiative will evaluate an alternative cervical cancer screening approach: self-collection of samples (self- sampling) by women, which are then sent to labs for human papillomavirus (HPV) testing. This approach aims to identify cervical cancer cases in these groups of women, which account for over half of cervical cancer cases in the United States each year. Self-sampling offers several benefits, including ease of collection at the time and place of the patient's choosing, without the need for a clinic appointment or speculum exam. To conduct this assessment, NCI established a public-private partnership between Federal agencies, industry partners, and professional societies/clinical guidelines organizations, and will support a nationwide, multicentric screening trial in diverse settings, the Last Mile Ini-

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[52] epi.grants.cancer.gov/eecc/.
[53] reporter.nih.gov/search/o5KPkwNzZUavBogOfHXfCgproject-details/10156374.
[54] reporter.nih.gov/search/frdhnx__EQkONjxE8GPyxvQ/project-details/9916725.
[55] reporter.nih.gov/search/-UP__KUgEu0G9__0Zt655Nsg/project-details/9961257.
[56] dceg.cancer.gov/research/cancer-types/cervix/cervix-mississippi.

tiative Self-sampling for HPV Testing to Improve Cervical Cancer Prevention Trial (LMI–SHIP Trial).[57]

Additionally, NCI is collaborating with the NIH Office of Research on Women's Health (ORWH) and other NIH Institutes and Centers to participate in an ORWH Advisory Committee on Research on Women's Health Consensus Conference to be held in October 2021. The conference will include a focus on cervical cancer disparities and research opportunities to continue to address disparities in incidence and mortality.

NCI will continue to identify opportunities to better understand and address cancer health disparities, including for cervical and uterine/endometrial cancers.

QUESTIONS SUBMITTED BY SENATOR RICHARD J. DURBIN

Question. Approximately 20,000 people in the United States have germline mutations in the gene RUNX1. Patients with RUNX1-familial platelet disorder are at a heightened risk for developing blood cancers. NCI supports a longitudinal natural history study of patients with such germline mutations and their families. While germline RUNX1 mutations are rare, I understand that NIH-funded research in this area holds promise for the fields of hematology and oncology.

How can deepening our understanding of, and ultimately developing cancer prevention strategies for, inherited blood cancer predisposition syndromes like RUNX1 familiar platelet disorder advance the entire cancer research field forward?

Answer. The RUNX1 gene regulates the development of blood cells (hematopoiesis), controlling other genes that help determine the fate of hematopoietic stem cells, which have the potential to develop into all types of mature blood cells, including platelets. Platelets are cells that help blood to clot. Inherited mutations in the RUNX1 gene cause familial platelet disorder with associated myeloid malignancies (RUNX1–FPDMM) and predispose individuals to some types of blood cancers. Although genetic predisposition to solid tumors such as breast and colon cancers has been widely recognized over the past several decades, the contribution of inherited genetic disorders related to blood cancer is a more recent field of study.

There are many instances where understanding the molecular basis for a rare inherited disease has provided insight into more common forms of a particular disease. For example, BRCA1 and BRCA2 mutations were discovered as hereditary breast cancer genes but are also relevant to sporadic (non-hereditary) breast cancers, ovarian cancers, and some hereditary forms of colon cancer. Similarly, understanding the blood cancers associated with RUNX1–FPDMM may lead to improved understanding of other types of blood cancers as well.

Research efforts across the National Institutes of Health (NIH) are underway to better understand RUNX1–FPDMM. Investigators funded by the National Heart, Lung, and Blood Institute (NHLBI) are studying cells from people with this disorder to better understand key target genes regulated by RUNX1 and their role in hematopoiesis.[58] This work could also yield a better understanding of genetic pathways that lead to blood cancers, as well as the blood clotting mechanisms that contribute to cardiovascular disease. Investigators at the National Human Genome Research Institute (NHGRI), along with intramural scientists at the National Cancer Institute (NCI), are conducting a natural history study at the NIH Clinical Center that is intended to identify and follow patients with RUNX1 mutations to hopefully identify biomarkers that can predict which patients will develop cancers.[59] To date, the study has enrolled 198 patients from 55 families, representing the largest FPDMM cohort being followed prospectively at a single institution in the world.

Studying RUNX1–FPDMM will have broader significance than just this rare disease. Germline (inherited) predisposition to hematopoietic malignancies is often under-diagnosed, with recent studies indicating that 10–30 percent of RUNX1 mutations detected in acute myeloid leukemias are inherited, which is much more common than previously appreciated.[60] In addition, FPDMM can serve as a model to study the development of leukemia, since researchers can monitor individuals with the RUNX1 mutation before they develop leukemia to identify factors associated with cancer risk and to map tumor evolution.

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[57] prevention.cancer.gov/major-programs/nci-cervical-cancer-last-mile-initiative.

[58] reporter.nih.gov/project-details/10083753.

[59] www.genome.gov/Current-NHGRI-Clinical-Studies/hematologic-and-premalignant-conditions-associated-with-RUNX1-mutation;clinicalstudies.info.nih.gov/ProtocolDetails.aspx?id=2019-HG-0059; clinicaltrials.gov/ct2/show/NCT03854318.

[60] pubmed.ncbi.nlm.nih.gov/32315381/.

QUESTIONS SUBMITTED BY SENATOR JACK REED

Question. The fiscal year 2021 Appropriations law included full funding—$30 million—for the Childhood Cancer STAR Act, which I authored.

Could you provide an update on how that funding will be spent in the coming year?

How will that work be coordinated with the childhood cancer data initiative?

Answer. NCI is supporting several new and ongoing Childhood Cancer STAR Act research projects in fiscal year 2021, for a total planned investment of $28 million. The Centers for Disease Control and Prevention continues to support enhancements to expand capacity within the National Program of Cancer Registries (NPCR) to help cancer registries collect and make the data on pediatric cancer cases available more rapidly, a $2 million effort in fiscal year 2021.

Consistent with provisions in Section 101 of the STAR Act, NCI's fiscal year 2021 appropriation for STAR Act activities is supporting new and expanded projects focused on the collection and storage of biospecimens for future research. Several projects are conducted through the NCI-supported Children's Oncology Group (COG) to focus additional attention to rare cancer subtypes that are currently underrepresented in NCI-supported biorepositories, as well as tumor types with a high risk of treatment failure. For example, particularly rare subtypes of pediatric cancers for which COG does not have open clinical trials, tumor tissue collection options are limited. STAR Act appropriations are supporting the COG Rare and Under-Represented Cancer Tissue Banking project to enable tumor tissue and associated germline (e.g., blood) sample collection for specific groups of patients for which current tumor tissue collection is lacking or inadequate, with priority for tumor types such as sarcomas and brain and central nervous system (CNS) tumors, which have high risk of treatment failure.

The COG Rare and Under-Represented Cancer Tissue Banking project was launched in fiscal year 2020 and is expanding in scope in fiscal year 2021. This initiative is collaborating closely with CCDI, and with the use of fiscal year 2021 CCDI funds, tumor tissue will undergo clinically-relevant molecular profiling through the CCDI Molecular Characterization Protocol. The data generated will be returned to treating physicians to help guide the diagnosis and treatment of patients, and the data will additionally be stored and made available to the research community through CCDI data platforms. In addition to rare cancer populations, the CCDI Molecular Characterization Protocol will initially support characterization of tumors from children with CNS tumors and from children with soft tissue sarcomas. The Protocol aims to collect, store, and make available detailed clinical and molecular information for each child participating in the study, including data that will help a pediatric oncologist treat that patient and help researchers learn more about childhood cancers.

NCI is continuing support in fiscal year 2021 for other STAR Act biobanking projects launched in fiscal year 2020. Through the COG Rapid Autopsy Specimen Collection project, NCI and COG are working with patient organizations to support rapid autopsy collection of tumor samples from children and adolescents and young adults (AYAs) who have died of their disease. Foundations and families within the pediatric brain tumor community have been leaders in such programs, and NCI continues to learn from their experiences to expand this model to other childhood cancers. We are incredibly grateful to these parents and caregivers, who amidst unimaginable grief and loss, contribute to future research to advance science and help other families.

NCI is also supporting the COG to continue to expand the collection of specimens taken at the time of relapse, as well as collecting diagnostic samples for children and AYAs who have already submitted samples at relapse through NCI's Pediatric Molecular Analysis for Therapy and Choice (MATCH) Precision Medicine Trial. An important impediment to understanding mechanisms of treatment failure for childhood solid tumors is the limited numbers of paired specimens from both diagnosis and relapse that are available for researchers to study. Specimens at relapse are critical for evaluating biological changes between diagnosis and relapse that can lead to the identification of mechanisms of treatment failure and to the development of strategies for circumventing these mechanisms. Through CCDI, Pediatric MATCH tumor specimens from diagnosis and from relapse are being molecularly characterized to identify the changes in gene mutations and gene expression that occur between diagnosis and relapse, which could inform better treatments.

Consistent with Section 202 of the STAR Act, in fiscal year 2021, NCI will continue to conduct and support childhood cancer survivorship research. NCI has supported two new Requests for Applications (RFAs) since fiscal year 2019 that are directly aligned with survivorship research areas emphasized in the STAR Act. Issued

in fiscal year 2019, RFA CA–19–033:[61] Improving Outcomes for Pediatric, Adolescent and Young Adult Cancer Survivors focused on projects to develop and test interventions that prevent, mitigate or manage adverse outcomes in pediatric and/or AYA cancer survivors and/or evaluate models of care that strengthen coordination, continuity, and quality, or that reduce access barriers to needed services including follow-up care, and that improve outcomes across the survivor's lifespan. Development of interventions to address disparities in outcomes and/or access to needed care, and to address the needs of minority or medically underserved pediatric and/or AYA populations were also prioritized. NCI is supporting seven awards in response to this RFA, and the awards will focus on various patient sub-populations (e.g. disease site), developmental groups, specific late and long-term effects, and the types of interventions (both preventive and supportive care).

Issued in fiscal year 2020, RFA CA–20–027[62] and RFA CA–20–028:[63] Research to Reduce Morbidity and Improve Care for Pediatric, and Adolescent and Young Adult (AYA) Cancer Survivors invite applications for research projects to improve care and health-related quality of life for childhood and AYA cancer survivors, with a focus on six key domains that align with research priorities emphasized in the STAR Act: (1) disparities in survivor outcomes; (2) barriers to follow-up care (e.g. access, adherence); (3) impact of familial, socioeconomic, and other environmental factors on survivor outcomes; (4) indicators for long-term follow-up needs related to risk for late effects, recurrence, and subsequent cancers; (5) risk factors and predictors of late/long-term effects of cancer treatment; and (6) development of targeted interventions to reduce the burden of cancer for pediatric/AYA survivors.

In fiscal year 2021, NCI will support subsequent years for grants initially awarded in fiscal year 2019 and fiscal year 2020, as awards were made for five-year terms, and the Institute will be making several new grant awards through the RFA launched in fiscal year 2020. The first round of applications is in the final stages of review, and awards will be made before the close of fiscal year 2021. The second round of applications are due on July 30, 2021, and awards are anticipated to be made in fiscal year 2022.

NCI also continues to make additional investments in childhood cancer survivorship research beyond the STAR Act appropriation, funding several notable initiatives and projects with resources provided through the Institute's general appropriation. For example, NCI continues to fund long-standing investments in the Childhood Cancer Survivor Study (CCSS),[64] which the Institute has supported continuously since establishing CCSS in 1994. This cohort of more than 38,000 childhood cancer survivors diagnosed between 1970 and 1999 (and 5,000 siblings of survivors who serve as the comparison group for the study) serves as a foundational resource for the survivorship research community.

Additionally, NCI continues to support research projects that investigators develop and submit independent of specific childhood and AYA cancer survivorship funding opportunities such as the STAR Act RFAs described above. These investigator-initiated research projects provide critical contributions to this field, and awards made to date in fiscal year 2021 include a project to compare symptom burdens (toxicity), neurocognitive change, and functional outcomes in children with pediatric brain tumors treated with proton versus photon radiotherapy. Proton beam radiotherapy (PBRT) is often thought to be a promising treatment for children with brain tumors as it may preserve cognitive functioning without sacrificing disease control. This will be the first large-scale study to prospectively compare the two therapies to assess important measures of daily functioning that will quantify the clinical significance of any differences identified between groups in survivorship. This project aims to help physicians and families better understand the relative effect of PBRT on symptoms and neurocognitive functioning to inform treatment decisions.[65] Another award is supporting further study of psychosocial risk in young survivors of pediatric cancer diagnosed in early childhood, including the role of both physical and neurocognitive late effects. This project aims to identify specific medical and neurocognitive late effects that increase psychosocial morbidity, as well as protective factors, to inform more effective interventions to optimize quality of life in children affected by cancers diagnosed in early childhood.[66] In addition, the NCI-supported ASPIRES (Activating cancer Survivors and their Primary care providers to Increase coloREctal cancer Screening) study aims to prevent the development of

[61] grants.nih.gov/grants/guide/rfa-files/RFA-ca-19-033.html.
[62] grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-027.html.
[63] grants.nih.gov/grants/guide/rfa-files/rfa-ca-20-028.html.
[64] cancer.gov/types/childhood-cancers/ccss.
[65] reporter.nih.gov/search/kPIDddsyREmcoShhVEYN4Q/project-details/10146799.
[66] reporter.nih.gov/search/5Nb7PgFn7kyHJnjYOFzMQA/project-details/10122486.

subsequent cancers among childhood cancer survivors treated with abdominal or pelvic radiotherapy, who are almost four times more likely to develop colorectal cancer (CRC) compared to the general population. The study will test a remote intervention aimed at promoting early CRC screening and detection.[67]

NCI remains committed to implementing the research sections of the STAR Act directed toward the Institute, and to ensuring that these efforts continue to complement the Institute's broader portfolio of childhood and AYA cancer research. This includes CCDI, the COG, the CCSS, and many other research programs and projects working together to support much needed progress for children with cancer and their families, including survivors and caregivers facing the challenges of managing the late effects of cancer and its treatments.

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

Question. Dr. Sharpless, one of the goals I had when I was Chairman of this Subcommittee was to increase NIH funding, in an effort to increase the success rates of grants—meaning more research grants would be funded. This is important because the NIH peer review system does not always reward high-risk science or young researchers' grant applications. But, if you have additional funding, you can fund more than just the 'safest' science grants from the most established researchers. NCI has seen an increase of more than 50 percent in the number of grant applications since 2013, keeping your success rates and paylines lower than most NIH Institutes. While the positive aspect of this statistic is that the cancer research community is energized and applying for NCI funding, you can only fund a certain amount of applications because of the significant increase in grant applications. The last two LHHS bills have included specific funding for NCI to increase their Research Project Grants.

How has this allowed you to increase success rates, raise the payline, and make more awards?

Answer. The intense competition and demand for NCI funding reflects incredible scientific opportunities in cancer research and presents a major challenge for the NCI to carefully balance increasing demand for competing grant funding while sustaining previous years' commitments to multi-year grants.

Investigator-initiated research has proven itself to be one of the biggest drivers of progress in cancer research, and accordingly is the biggest driver of NCI's budget, with long-term investments into funding new and continuing awards constituting more than 40 percent of NCI's annual budget. These awards have been the source of some of the most innovative and transformative ideas in cancer research, leading to direct benefits for patients in the form of new oncology drug approvals, the development of immune checkpoint inhibitor therapy (Nobel Laureate Jim Allison), CAR–T (chimeric antigen receptor-T) cell immunotherapy (Carl June), and novel drug design strategies such as PROTACs (proteolysis targeting chimeras)[68] that use normal cellular processes to identify and destroy proteins in cancer cells that drive cancer growth (Raymond DeShais and Craig Crews).

Considering all funding mechanisms, NCI supported 109 additional awards in fiscal year 2020 as compared to fiscal year 2019 (from 6,053 in fiscal year 2019[69] to 6,162 in fiscal year 2020[70]). Across fiscal year 2020 and 2021, the successive funding increases allowed NCI to increase the R01 payline from the 8th percentile in fiscal year 2019 to the 11th percentile in fiscal year 2021. With the fiscal year 2020 budget increase, NCI increased R01 paylines by 25 percent compared to fiscal year 2019 and restored continuing grants to 100 percent of their committed level, providing researchers the full fiscal year 2020 budget approved during the initial grant award. Funding increases in fiscal year 2021 allowed NCI to further raise the payline for R01 research awards, for an overall 35 percent increase compared to 2019, as well as to keep funding continuing awards at 100 percent. In addition, for those two consecutive years (fiscal year 2020 and fiscal year 2021), NCI also raised the payline for Early-Stage Investigators, reflecting NCI's commitment to developing and supporting early career scientists to build the next generation of cancer researchers.

We have the final success rate and total number of awards results for fiscal year 2020, the year when Congress targeted an additional $212.5 million for new and

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[67] reporter.nih.gov/search/5Nb7PgFn7kyHJnjYOFzMQA/project-details/10096080.

[68] www.cancer.gov/research/annual-plan/scientific-topics/protac-infographic.

[69] www.cancer.gov/about-nci/budget/congressional-justification/fy2021-nci-congressional-justification.pdf.

[70] www.cancer.gov/about-nci/budget/congressional-justification/fy2022-nci-congressional-justification.pdf.

continuing grants, but we will not have final results for fiscal year 2021 until after the first quarter of fiscal year 2022. Our fiscal year 2020 results show that NCI increased the number of competing R01s we issued within the payline by more than 100 awards, a jump of more than 15 percent from the prior year. The funding increase also allowed us to pay other meritorious R01 applications that scored just outside the payline. Overall, our success rate for fiscal year 2020 rose to 12.7 percent, from 11.6 percent in the prior year.

The targeted increases that Congress has provided allows NCI to increase paylines, achieve a corresponding increase in the overall NCI application success rate, and issue more grant awards. This funding has been critical to awarding new grants, while also allowing NCI to support ongoing research and the breadth of core NCI research investments, such as NCI's designated cancer centers, Specialized Programs of Research Excellence (SPOREs), and large national networks of clinical trials. All of these awards and programs will continue to fuel broad, sustained progress that serves the needs of individuals with cancer and those at risk of cancer, leading to a deeper understanding of the biology of cancer and new strategies to prevent, screen, diagnose, and treat cancer, in all its forms.

QUESTIONS SUBMITTED BY SENATOR SHELLEY MOORE CAPITO

Question. The NCI is doing tremendous work in implementing the new Childhood Cancer Data Initiative, which holds the promise of vastly improving the treatment of childhood cancer and the quality of life for survivors. The Childhood Cancer STAR Act calls for a major investment in biorepository and bio-specimen collection.

Can you tell us how these two vital initiatives are working together? NIH Response:

Answer. The National Cancer Institute (NCI) agrees that it is vital for biospecimen collection and storage efforts supported through the STAR Act and data generation, analysis, and sharing supported through Childhood Cancer Data Initiative (CCDI) to continue to contribute to and enhance each initiative's progress in a complementary manner. To that end, NCI is utilizing STAR Act appropriations to support the Children's Oncology Group (COG) Rare Tumor Populations Biobanking project, which enables tumor tissue and germline (e.g., blood) collection for specific groups of patients for which current tumor tissue collection is lacking or inadequate, with priority for tumor types such as sarcomas and brain and central nervous system tumors, which often have the highest risk of treatment failure.

The COG Rare Tumor Populations Biobank was launched in fiscal year 2020 and is expanding in scope in fiscal year 2021. This initiative is collaborating closely with CCDI, and with the use of fiscal year 2021 CCDI funds, tumor tissue will undergo clinically-relevant molecular profiling through the CCDI Molecular Characterization Protocol. The COG Rare Tumor Populations Biobank provides a critical foundation for these characterization efforts within CCDI. The data generated will be returned to treating physicians to help guide the diagnosis and treatment of patients, and the data will be stored and made available to the research community through CCDI data platforms. In addition to rare cancer populations, the CCDI Molecular Characterization Protocol will initially support characterization of tumors from children with Central Nervous System (CNS) tumors and from children with soft tissue sarcomas. The Protocol aims to collect, store, and make available detailed clinical and molecular information for each child participating in the study, including data that will help a pediatric oncologist treat that patient and help researchers learn more about childhood cancers.

NCI is also supporting a STAR Act biobanking project through the COG to continue to expand the collection of specimens taken at the time of relapse, as well as collecting diagnostic samples for children and adolescents and young adults (AYAs) who have already submitted samples at relapse through NCI's Pediatric Molecular Analysis for Therapy and Choice (MATCH) Precision Medicine Trial. An important impediment to understanding mechanisms of treatment failure for childhood solid tumors is the limited numbers of paired specimens from both diagnosis and relapse that are available for researchers to study. Specimens at relapse are critical for evaluating biological changes between diagnosis and relapse that can lead to the identification of mechanisms of treatment failure and to the development of strategies for circumventing these mechanisms. Through CCDI, Pediatric MATCH tumor specimens from diagnosis and from relapse are being molecularly characterized to identify the changes in gene mutations and gene expression that occur between diagnosis and relapse, which could inform better treatments.

These are specific examples of early and ongoing collaboration between STAR Act and CCDI- supported projects, and more broadly, there will be additional opportuni-

ties for data generated through STAR Act specimen collection and survivorship research efforts to contribute to the CCDI data ecosystem. For example, other STAR Act biobanking projects have supported additional biospecimen collection within the NCI-supported Childhood Cancer Survivor Study (CCSS), focused on subsequent cancers and chronic health conditions. CCDI funds were used to molecularly characterize specimens from patients who developed second cancers to enhance understanding of the genetic factors that lead to increased risk of second malignant tumors. Additionally, CCDI funds have supported submission and management of CCSS data to NCI and other NIH repositories so that they can be linked within the CCDI data ecosystem and more easily shared with the broader research community.

As NCI's CCDI continues to link data resources across the childhood cancer research field, we envision these linkages and the data ecosystem they create serving as a resource for continued research, and as a growing repository for all types of data generated through NCI and other funded childhood and AYA cancer research. Similar to the CCSS, individual research projects, including preclinical studies and clinical trials, will have the opportunity to contribute data to CCDI, linking this additional data to CCDI resources such as the Molecular Characterization Protocol and the National Childhood Cancer Registry, two foundational CCDI initiatives.

QUESTIONS SUBMITTED BY SENATOR CINDY HYDE-SMITH

Question. I, along with many members of the committee remain concerned with the lack of targeted therapies for rare cancer patients. It is my understanding that rare cancers account for 380 of 400 distinct forms of cancer and almost 1/3 of all diagnoses and include all pediatric cancers. A recent analysis showed that 80 percent of all patients who lacked an FDA-targeted therapy were rare cancer patients. In addition, of the 3,994 clinical trials in phases 1, 2, and 3 from January 1, 2012 to January 1, 2017, almost 75 percent did not include a rare cancer by name. While rare cancer affects every population, translational research and commercial drug development has traditionally neglected small patient populations. Each subtype of cancer requires a targeted therapy in order to save a life or to significantly improve lifespan.

What is NIH's plan to ensure there are adequate investments for treatments for rare cancer patients and what can Congress and this committee do to help?

Answer. The National Institutes of Health (NIH) remains committed to supporting research to advance the understanding of all cancers, including rare cancers, and to inform the development of targeted cancer therapies for rare cancers and rare subtypes of cancers, including pediatric cancers (all types and subtypes of pediatric cancers are considered "rare" by definition).

The cancer research community—thanks to NIH-supported developments in understanding the specific genes, proteins, and other unique molecular characteristics driving certain cancer subtypes—continues to recognize that cancer is made up of a collection of hundreds, if not thousands, of subtypes defined by these characteristics. As a result of National Cancer Institute (NCI)-supported efforts and other relevant research, "cancer" is increasingly becoming a collection of rare cancer subtypes.

This evolved understanding of cancer is reflected in NCI's current clinical trials portfolio and investments in translational and basic research, including several initiatives in the intramural Center for Cancer Research (CCR).

Increasingly, clinical trials are examining targeted therapies based on molecular subtypes. For example, NCI's National Clinical Trials Network (NCTN) is currently supporting trials assessing therapies to treat gliomas with certain genetic alterations [71] and pancreatic cancers with specific gene alterations.[72,73] NCI also supports trials that are dedicated to patients with rare tumors, including the NCTN-supported Dual Anti-CTLA–4 and Anti-PD1–Blockade in Rare Tumors (DART) Trial [74] and the Rapid Analysis and Response Evaluation of Combination Anti-Neoplastic Agents in Rare Tumors (RARE CANCER) Trial,[75] which is supported by NCI's Experimental Therapeutics Clinical Trials Network.

To ensure that researchers have a strong pipeline of therapy candidates to consider for use in clinical trials, NCI supports several initiatives to support the preclinical stage of development of therapeutics to treat rare cancers, including the NCI

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[71] www.clinicaltrials.gov/ct2/show/NCT00887146.
[72] www.clinicaltrials.gov/ct2/show/NCT04858334.
[73] www.clinicaltrials.gov/ct2/show/NCT04548752.
[74] www.clinicaltrials.gov/ct2/show/NCT02834013.
[75] www.clinicaltrials.gov/ct2/show/NCT04449549.

Experimental Therapeutics (NeXT) Program and the Pediatric Preclinical Testing Consortium (PPTC). The mission of NeXT is to advance clinical practice and bring improved therapies to patients with cancer by supporting the most promising new drug discovery and development projects. The PPTC addresses key challenges associated with the development of new therapies for children with cancer by developing reliable preclinical testing data for pediatric drug candidates that can be used to inform new agent prioritization decisions.

The first step in identifying new therapeutic targets, however, is elucidating the basic biological mechanisms that give rise to cancers. To further these research efforts, NCI supports the development of resources for broad use across the cancer research community. These resources include cell lines, organoid models, patient derived xenograft (PDX) models, biospecimens, and other biological samples. NCI makes drug information summaries available on its website, along with extensive cancer treatment summaries. Additional resources include the Developmental Therapeutics Program, the National Clinical Trials Network (NCTN) Navigator, Patient-Derived Xenograft (PDX) Centers, PDX Finder, the NCI Mouse Repository, and the Physician Data Query (PDQ) Database.[76]

The Rare Tumor Patient Engagement Network, launched in fiscal year 2018 and part of NCI's CCR, leverages the resources of the NCI intramural research program and the NIH Clinical Center to bring together investigators, patients, and advocacy groups to study rare tumors. Under the umbrella of this effort, NCI launched the My Pediatric, Adolescent, and Adult Rare Tumor (MyPART) Network, a collaboration of scientists, patients, family members, advocates, and healthcare providers to find treatments for rare cancers. The MyPART Network collects samples like blood, saliva, and archived biopsy tissue from people with rare solid tumors as part of the Natural History Study of Rare Solid Tumors. The purpose of the study is to engage rare tumor patients and their families in the research process, study how rare tumors grow, track participants' health history over a long period of time, share data with other scientists, build new ways of testing new treatments, and design new clinical trials for rare cancers. MyPART scientists also hold clinics on rare tumors to facilitate collaborations between researchers, patients, and advocacy organizations; to date, MyPART has hosted clinics on chordomas, SDH-deficient gastrointestinal stromal tumors, and medullary thyroid cancer, and more clinics are in the planning stages. Additionally, the NCI Comprehensive Oncology Network Evaluating Rare CNS Tumors (NCI–CONNECT) 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; seven clinical studies and trials are currently open through NCI–CONNECT.[77]

Because of these and similar investments, the U.S. Food and Drug Administration (FDA) has approved a number of therapies in recent years for patients with rare cancer subtypes and related conditions. For example, in May 2021, the FDA granted accelerated approval to sotorasib (Lumakras) for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with alterations in the KRAS G12–C gene, a mutation which is present in only 13.8 percentsa of NSCLC patients. Similarly, the FDA approved selumetinib (Koselugo) in 2020 for the rare tumor condition neurofibromatosis type 1, in patients over the age of two, as the first approved treatment for this condition. In 2018, the FDA granted accelerated approval to larotrectinib (Vitrakvi) for adult and pediatric patients with solid tumors with a neurotrophic receptor tyrosine kinase (NTRK) gene fusion. NTRK gene fusions are prevalent in nearly all cases of certain rare cancer subtypes, including secretory carcinoma of the breast or salivary gland and infantile fibrosarcoma; they have also been observed in some patients with more common types of cancer, such as glioma, melanoma, and carcinomas of the thyroid, lung, and colon.[78]

NIH will continue to support research efforts that reflect the scientific understanding of the many subtypes of cancers, including work that will enable the development of therapies for rare tumor subtypes.

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[76] A more extensive list is available at www.cancer.gov/research/resources/.
[77] www.cancer.gov/rare-brain-spine-tumor/refer-participate/clinical-studies.
[78] www.ncbi.nlm.nih.gov/pmc/articles/PMC6859817/.

QUESTIONS SUBMITTED TO DR. GARY GIBBONS

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

Question. Dr. Gibbons, we have all heard about the plight of COVID–19 "long-haulers" who have symptoms after their acute COVID–19 infection has subsided. A growing number of studies suggest that many patients experience some type of heart damage after contracting the infection, even in those not sick enough to be hospitalized. According to the American Heart Association, nearly one-fourth of those hospitalized with COVID–19 have been diagnosed with cardiovascular complications. A study in the Journal of the American Medical Association stated that researchers found abnormalities in the hearts of 79 percent of recovered patients and "ongoing myocardial inflammation" in 60 percent.

Who is most at-risk of this type of heart damage, and is there indication that this damage is permanent?

With heart damage appearing to be widespread, will screenings to detect cardiovascular damage be included as routine follow-up care for COVID–19 patients?

Do you have any sense of how long longitudinal studies should last to follow long-haulers?

Answer. While severe acute respiratory syndrome coronavirus 2 (SARS–CoV–2) enters the body through the respiratory tract, the virus also infects many other cell types and can damage multiple organs and tissues, including the heart and blood vessels. In rare cases, acute infection has been associated with cardiovascular complications including acute myocardial injury, myocarditis (heart inflammation), and arrhythmias (irregular heartbeat). This is not surprising given that viruses frequently trigger inflammation, and as the body's immune system fights off the virus, the inflammatory process can damage healthy tissues, including the heart. Many different viruses are known to cause myocardial injury and myocarditis.

Many patients with coronavirus disease 2019 (COVID–19) experience damage to their blood vessels, leading to the formation of blood clots (thrombosis) that can develop in or travel to vital organs, including the heart. Blood clots in the coronary arteries can starve the heart of oxygen and damage the heart muscle. NIH's ACTIV–4 Antithrombotics adaptive master protocols have made progress in evaluating the safety and effectiveness of various types of blood thinners (e.g., aspirin, heparin, apixaban) for treating adults with signs of blood vessel damage and thrombosis from COVID–19, known as COVID–19-associated coagulopathy.[79] Clinical trials are ongoing across three patient populations (inpatient, outpatient, and convalescent or patients recovering from COVID–19). These trials are providing valuable information about how to help prevent moderately ill patients with COVID–19 from progressing to intensive care, and could perhaps help mitigate future cardiac complications. For example, ACTIV–4 has shown that full-dose heparin is safe and effective at preventing blood clots in moderately ill hospitalized patients and reduced the need for life support.

Studies have shown that patients with COVID–19 may show signs of cardiac injury, detected by a release of the cardiac muscle protein troponin into the bloodstream.[80] Such injury is associated with worse short-term outcomes and higher mortality. An analysis of more than 40 studies involving more than 8,000 COVID–19 patients found that venous thromboembolism (VTE; blood clots originating in a vein) occurred in approximately 21 percent of patients.[81] Among COVID–19 patients admitted to intensive care, the VTE rate was as high as 31 percent. A review of myocarditis associated with acute COVID–19 estimated that the incidence is less than five percent; although less than previously thought, this could still mean a large number of patients with acute myocarditis given that COVID–19 cases in the United States have surpassed 33 million.

The incidence of continuing or new cardiac problems after COVID–19 or asymptomatic SARS–CoV–2 infection remains unknown. Although most people with COVID–19 get better within weeks of illness, some people experience post-acute sequelae, including chest pains, shortness of breath, exhaustion, heart palpitations, and chest pain. In addition, patients diagnosed with cardiac injury, thrombosis, or myocarditis during acute COVID–19 could sustain damage to the heart that persists long after the acute illness has passed. There is still much to be learned about the long-term cardiovascular consequences of SARS–CoV–2 infection.

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[79] www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ4.

[80] www.heartrhythmjournal.com/article/S1547-5271(20)30625-1/fulltext#tbl1.

[81] pubmed.ncbi.nlm.nih.gov/33251499/.

NIH's Researching COVID to Enhance Recovery (RECOVER) initiative seeks to understand, and ultimately to prevent and treat, long COVID and other post-acute sequelae of SARS–CoV–2 (PASC) across the lifespan.[82] At the center of the Initiative is an observational study that will include adults and children recruited from ongoing studies of COVID–19, long COVID clinics, and other cohorts. RECOVER is designed to significantly expand both our knowledge about the full clinical spectrum, long term outcomes, and underlying biology of PASC; as well as our ability to provide safe and effective therapeutic interventions.

Current diagnostic protocols generally include physical, cognitive, and psychological assessments. The evaluation of patients hospitalized with COVID–19 includes elements of a cardiovascular evaluation, including assessment of known cardiovascular disease and risk factors for cardiovascular disease, assessment of symptoms that may be caused by respiratory or cardiac disease, laboratory testing (including a complete blood count and complete metabolic panel), chest radiograph, electrocardiogram (ECG), and troponin testing (which is followed if elevated). A more targeted cardiac evaluation may be needed depending on the patient's symptoms. Patients who develop new onset heart failure, for example, may need an echocardiogram (echo) to determine the best course of action. One of the goals of the RECOVER meta-cohort study is to develop core defining characteristics and diagnostic criteria for long COVID and other forms of post-acute sequelae of SARS–CoV–2 infection (PASC), including understanding the impact the virus has on the cardiovascular system.

NIH plans to, and has support to follow the RECOVER meta-cohort for at least 3 years. In addition to addressing the public health impact of SARS–CoV–2 infection, RECOVER also has the potential to enhance our understanding of other chronic syndromes theorized to have a viral origin, at least in some individuals, such as chronic fatigue syndrome and postural orthostatic tachycardia syndrome (POTS).

QUESTIONS SUBMITTED BY SENATOR SHELLEY MOORE CAPITO

Question. Pulmonary fibrosis (PF) means scarring in the lungs. Over time, the scar tissue can destroy the normal lung and make it hard for oxygen to pass through the walls of the air sacs into the bloodstream. PF is not just one disease—it is a group of more than 200 different lung diseases that all look very much alike.

The most recent studies show that more than 200,000 Americans are living with PF today. Approximately 50,000 new cases are diagnosed each year and as many as 40,000 Americans die each year. With no known cure, certain forms of PF, such as idiopathic pulmonary fibrosis, (IPF), may take the lives of patients within three to 5 years from diagnosis.

PRECISIONS is the first-ever clinical trial to apply the principles of precision medicine to the diagnosis and treatment of idiopathic pulmonary fibrosis. PRECISIONS is supported by a $22 million grant from the National Institutes of Health (NHLBI grant number HL145266) and Three Lakes Foundation, a philanthropic organization.

PRECISIONS is designed as a double-blind, multi-center, randomized, placebo-controlled trial investigating the safety and efficacy of NAC in patients with IPF who have a specific genetic variant which is present in 25 percent of IPF patients. The trial will enroll 200 patients from approximately 20 PFF Care Center Network (CCN) sites. Initial recruitment into the study is being facilitated by looking at phenotypic data from patients that are enrolled in the PFF Registry.

Can you provide an update on the NHLBI-funded PRECISIONS grant, which seeks to shed more light on the role of genetics in pulmonary fibrosis?

How has the COVID pandemic affected this study?

Answer. The National Heart, Lung, and Blood Institute (NHLBI) is committed to supporting research on pulmonary fibrosis, which leads to progressive scarring of the lungs that makes it increasingly more difficult to breathe. PRECISIONS[83] is a five-year study that aims to enroll 200 patients with idiopathic pulmonary fibrosis (IPF) and use genetic testing to identify those patients most likely to respond to an experimental treatment, an antioxidant known as N-acetylcysteine or NAC. This first-of-its-kind precision medicine trial builds on an earlier study suggesting that a gene called TOLLIP influences how patients respond to NAC, such that it might be helpful only for a subgroup of patients who have a particular version of the gene.

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[82] recovercovid.org/.

[83] reporter.nih.gov/project-details/9822535.

The trial will enroll only that subgroup, in order to increase the likelihood of detecting a benefit.

PRECISIONS is co-funded by the Three Lakes Foundation, a non-profit philanthropy that supports education and research efforts to improve the time to diagnosis and accelerate new therapies for IPF. The study also involves a partnership with the Pulmonary Fibrosis Foundation, whose patient registry is being leveraged to perform molecular analyses on biospecimens obtained from patients with IPF. These analyses are intended to uncover novel genetic risk factors that will improve IPF diagnosis, predict its clinical course, and understand its underlying disease mechanisms—all of which could yield further insight into potential targeted therapies.

The study was delayed in the latter half of fiscal year 2020 due to COVID–19-related institutional research restrictions, which led to NHLBI approval of a six-month interim no-cost extension. By December 2020, the investigators had successfully completed all pre-specified project milestones for the first phase of their biphasic research plan, including enrollment of the first study participant. NHLBI approved the transition to the second phase of the project in March 2021. To date, six study sites have been activated, the percentage of eligible participants who meet the study's genotype inclusion criteria has been exactly as expected, and recruitment has proceeded on target.

During COVID–19-related delays and uncertainty regarding the feasibility of in-person lung function assessments (spirometry), PRECISIONS initiated an ancillary study to understand the utility of home spirometry to monitor patients with IPF. The study also intends to add a COVID–19—specific questionnaire to baseline and follow-up visits in the clinical trial as a means of leveraging this existing patient cohort to capture additional data on the epidemiological and clinical characteristics of COVID–19.

QUESTIONS SUBMITTED BY SENATOR CINDY HYDE-SMITH

Question. Concerned about other countries' ability to obtain vaccines quickly for their populations, the Administration recently announced that it will support a waiver of the World Trade Organization TRIPS Agreement, which would waive intellectual property protections for COVID–19 vaccines. It is my understanding, however, that there are no guarantees that the companies or countries who seek to use vaccine manufacturer's intellectual property to make copies will be able to deliver safe and effective vaccines, or that their manufacturing processes will meet the strict regulatory standards necessary for authorization. Furthermore, there are already reports of counterfeit vaccines being used to exploit vulnerable populations in the U.S. and around the world.

Are you concerned that giving away intellectual property via a TRIPS waiver could make worse the problem of counterfeit and low-quality vaccines in the market? What effect could this have on endangering lives and undermining public confidence in the vaccines that have been proven safe and effective?

Answer. The National Institutes of Health (NIH) is concerned about counterfeit and low-quality vaccines; however, NIH does not have the expertise or authority to investigate these matters. The degree to which any TRIPS waiver addresses these issues of concern will not be known unless and until the terms are agreed upon.

Question. The Administration recently endorsed the idea of waiving intellectual property (IP) protections for COVID–19 vaccines, in the hopes that it will speed up manufacturing of the vaccines around world. However, it is my understanding that some vaccine developers are already experiencing constraints in everything from raw materials to fill-finish capacity critical to producing and administering vaccines.

Are you concerned that diverting critical supplies from manufacturers with proven track records for delivering high-quality, safe and effective vaccines could actually worsen the supply chain constraints we're currently seeing, and not just for COVID vaccines, but also non-COVID–19 medicines such as oncology and other infectious diseases?

Answer. The National Institutes of Health (NIH) fully supports efforts to ensure reliable supply chains for vaccines and other medicines; however, NIH is not directly involved in these efforts.

QUESTIONS SUBMITTED TO DR. PÉREZ-STABLE

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

Question. Dr. Pérez-Stable, we typically talk about getting researchers into the NIH field and staying there as a pipeline. However, when we look at the pipeline

for minority researchers, it can easily be called a funnel. We have a lot of work to do in increasing the diversity of NIH researchers. And as the COVID–19 pandemic has highlighted, NIH must also focus on health disparities research. The problems to these two solutions may go hand-in-hand. I know that Dr. Collins has started the UNITE program to look at racial inequities within the NIH community and has started a Common Fund program to fund transformative research into health disparities. While I commend these steps, many of the fundamental issues these programs are trying to address are reasons we started the Institute you fund—the National Institute for Minority Health and Health Disparities.

Can you provide your perspective on how we get more minority scientists into the NIH community?

And, specifically, what role should NIH take in making sure minorities have the educational background necessary to go into STEM fields—which often starts at the high school level, if not earlier?

Answer. The National Institutes of Health (NIH) is committed to diversifying the research workforce and will continue to identify opportunities to increase its focus on building and supporting a diverse scientific workforce. The NIH UNITE initiative was developed to address inequity in biomedical research and will help NIH to identify more strategies and opportunities to strengthen its efforts to diversify the research workforce and attract and prepare more students from underrepresented backgrounds for STEM careers. The NIH already has several efforts to diversify the STEM pipeline and to train students at all levels of education as described below.

NIH supports several initiatives to attract and recruit more minority scientists into the NIH intramural community. For example, the NIH Equity Committee systematically tracks and evaluates diversity, inclusion, and equity metrics in the intramural research program. In addition, the Distinguished Scholars Program (DSP) enhances the diversity of principal investigators in the NIH Intramural Research Program (IRP) by supporting first year tenure-track investigators with supplemental funds to start their research lab and engaging in activities designed to foster a sense of belonging and to promote research and career success. Moreover, the IRP provides a diverse environment for NIH-wide scientific recruitments through the Stadtman Tenure-Track Investigators, Lasker Clinical Research Scholars, and Early Independent Scientists recruitment programs. This approach has led to a greater proportion of women and scientists from underrepresented backgrounds recruited to NIH. The 2019 DSP cohort was comprised of approximately 7 percent Hispanics or Latinos, 27 percent African Americans or Blacks, 27 percent Asians, 40 percent White, and 73 percent female. Among the fiscal year 2020 cohort, 21 percent was African American or Black, 21 percent Hispanic or Latino, 21 percent Asian, 36 percent White, and 50 percent female. Of the 15 Distinguished Scholars selected in the 2019 cohort, nine were Stadtman Tenure-Track Investigators, and two were Lasker Clinical Research Scholars. Of the 14 Distinguished Scholars selected in the 2020 cohort, 10 were Stadtman Investigators, and three were Lasker Scholars.

Extramurally, NIH has dedicated efforts to recruit diverse scientists from underrepresented groups to prepare successful NIH grants. NIH provides Diversity Research Supplements to enhance the diversity of the research workforce by recruiting and supporting graduate students, post-doctoral fellows, and eligible investigators from diverse backgrounds, including those from groups that have been shown to be underrepresented in health-related research. These supplements to existing grants provide a pathway to career success for scientists from diverse backgrounds and remains relatively underutilized. There are several other NIH programs that promote diversifying the research workforce and some are highlighted below. First, the NIH/National Institute on Minority Health and Health Disparities Loan Repayment Program (NIMHD LRP), which aims to increase the pool of qualified researchers who conduct health disparities research. Over a 15-year period, recipients of an LRP award from NIMHD are more likely to be awarded a subsequent NIH grant than their counterparts who were not successful. The LRP Health Disparities applications have now been extended to all NIH Institutes as of 2019. Second, the Native American Research Centers for Health promote a cadre of scientists and health research professionals interested in American Indian/Alaska Native health research. Third, NIMHD established the NIMHD Health Disparities Research Institute to support the research career development of promising early-career minority health and health disparities research scientists. Fourth, the NIH's Faculty Institutional Recruitment for Sustainable Transformation (FIRST) program, announced in 2020, will increase the participation of researchers dedicated to inclusive excellence, including minority researchers, in biomedical research at NIH-funded institutions. The aim of the program is to enhance institutional inclusive excellence, with diversity and equity at its core enabling biomedical research institutions to hire a diverse cohort of early-stage research faculty committed to inclusive excellence and diver-

sity. The current pipeline of underrepresented scientists is not empty with about 14 percent of new U.S.-granted Science, Technology, Engineering and Math (STEM) PhDs awarded to underrepresented groups and similarly 14 percent of current medical students are from these groups.Lastly, the Science Education Partnership Award (SEPA) Program funds innovative pre-kindergarten to grade 12 science, technology, engineering, and mathematics (STEM) and Informal Science Education (ISE) educational projects. SEPA projects create partnerships among biomedical and clinical researchers and teachers and schools, museums and science centers, media experts, and other educational organizations. The NIH will continue to identify opportunities to increase its focus on building and supporting a diverse scientific workforce.

SUBCOMMITTEE RECESS

Senator MURRAY. The meeting is adjourned. Thank you.

[Whereupon, at 12:08 p.m., Wednesday, May 26, the subcommittee was recessed, to reconvene subject to the call of the Chair.]