

**DEPARTMENTS OF LABOR, HEALTH AND
HUMAN SERVICES, AND EDUCATION, AND
RELATED AGENCIES APPROPRIATIONS FOR
FISCAL YEAR 2023**

TUESDAY, MAY 17, 2022

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

The subcommittee met at 10:02 a.m. in room SD-138, Dirksen Senate Office Building, Hon. Patty Murray (chairwoman) presiding.
Present: Senators Murray, Durbin, Reed, Baldwin, Blunt, Moran, Kennedy, Braun, and Rubio.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

STATEMENT OF LAWRENCE TABAK, D.D.S., PH.D., ACTING DIRECTOR

ACCOMPANIED BY:

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

GARY GIBBONS, M.D., DIRECTOR, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

JOSHUA GORDON, M.D., PH.D., DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH

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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 2023 budget request for the National Institutes of Health.

Senator Blunt and I will each have an opening statement. Then I will introduce our witnesses. And after their testimony, Senators will each have 5 minutes for a round of questions.

While we were unable to have this hearing fully open to the public, or media for in-person attendance, live video is available on our committee website. If you are in need of accommodations, including

closed captioning, you can reach out to the Committee or the Office of Congressional Accessibility Services.

Every day across my Home State of Washington, researchers at the Fred Hutch Center, University of Washington, Washington State University, Seattle Children's hospital, and so many other world-class institutions are working around the clock and making ground-breaking discoveries.

Discoveries that don't just drive innovation and economic growth, but also bring families, cures, and treatments, and hope for the future, discoveries that saves lives, discoveries that don't just drive innovation and economic growth, but also bring families cures, and treatments, and hope for the future.

I am pleased to say this budget request shows the administration understands the tremendous importance of supporting our Nation's biomedical research community, and continuing our tradition of global leadership here, especially as in the past few years, have been such a stark reminder of how the investments we make in research today pay off down the road.

The rapid development of safe, effective COVID vaccines was made possible by research into mRNA vaccines we funded, in response to Ebola and other viruses, and by a biomedical research enterprise that has been built over decades.

And today, thanks to the vaccines and therapeutics that NIH (National Institutes of Health) researched to help develop, COVID deaths and hospitalizations are the lowest we have seen in 2 years. However, we are not out of the woods yet when it comes to this pandemic. There is still the threat of new, more deadly variants, especially right now when caseloads are inching up again, but our communities' resources have largely been spent down.

We need to defend the hard-won progress we have made, and that means passing emergency COVID funding, so our communities have the tests, and treatments, and vaccines, and tools they need to keep families safe.

This is really urgent. So I am going to keep fighting to make sure we get it done. And in addition to providing our communities the resources they need to fight this pandemic, I hope we are able to come together this year, as we have so many times in the past, to continue providing our researchers what they need to help us to fight COVID-19, and so many other challenges.

Challenges like: Developing better tests, making next-generation vaccines that are effective against all COVID variants, and understanding long COVID, and how we support the millions of people who are living with it; and challenges like the mental health crisis this pandemic has made so much worse, especially for young people, or overdose deaths which have been skyrocketing due to the rise of fentanyl.

Recently, our Nation lost a record 107,000 people to overdose deaths in a single year, and in Washington State, opioid deaths increased by two-thirds in 2021. This crisis is tearing a hole in so many communities, so many families, it is truly heartbreaking, and we have to pull out all the stops to get this under control.

That is why I am working on bipartisan legislation to strengthen programs that help our first responders, healthcare professionals,

and others on the front lines. And why I want to make sure we continue investing in research here like this budget proposes.

Of course the measure of success against any disease is not how much we invest to fight it; it is how much we are helping patients. For example, when it comes to Alzheimer's disease, that is exactly what we need to be focused on, for patients fighting this disease the stakes are intensely personal. They are fighting to hold onto cherished memories with loved ones, and a feeling of control over their daily lives, and the weight of that fight falls on their family members, friends, and caregivers.

With so much at stake in their lives, these families deserve to know the research projects they are depending on are being thoughtfully designed and prioritized for meaningful outcomes and results. This is really important for me, especially when we have increased funding for Alzheimer's research six-fold since 2015; when the 2025 target date that is established in the National Alzheimer Project Act is just around the corner, and when there are so many other terrible diseases families are desperate for NIH to put more resources into as well.

Another important undertaking is the launch of the Advanced Research Projects Authority for Health, which aims to break the mold for how cutting-edge research is conducted, speed up the discovery and development of medical treatments, and support projects that have the potential to transform medicine.

I worked hard to provide resources to establish ARPA-H (Advanced Research Projects Agency for Health) in our bipartisan funding bill earlier this year, and I am working hard right now to pass the Prevent Pandemics Act to set it up for long-term success.

That requires striking a balance to ensure ARPA-H can complement NIH's expertise while still operating independently to nimbly seize opportunities to accelerate innovation and breakthroughs.

I am focused on getting that balance right, so I will be asking more about why so much of the NIH budget increase, requested by the administration, goes towards ARPA-H when it is yet to bring on a staff and what that means for the other NIH institutes and centers.

Of course at the end of the day, innovation isn't 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 this work is to our families, we can't afford to have this agency's potential limited, or its success threatened by bias, discrimination, or harassment in the workplace.

We have to do more to address harassment in the biomedical research community, as well as address the fact that the number of researches of color is too low, and even clinical trials often fail to be adequately representative.

These are real problems with real consequences for research, and I have been pressing for progress on this for years. So I have been glad to see NIH working to examine barriers to diversity among its researchers, address how its practices have reimbursed structural biases and discrimination, and implementing a new policy, as secured in this committee that requires those that receive NIH grants to notify the agency when a Principal Investigator is removed, even temporarily, for sexual harassment or bullying.

But more work remains to be done to remove racism, discrimination, and harassment from research. And I will continue to follow our progress here.

Finally, before I turn over to Senator Blunt, I just want to take a moment to note that this will be the last NIH hearing we have with him, and to say how grateful I am, Senator Blunt, for all the work with you on this issue over the years.

It has been really great to have a partner across the aisle who really understands why these investments are so important to families, in Washington State, Missouri, across the country, and who is really willing to sit down and work in a bipartisan way to make sure we are delivering for folks back home.

So thank you so much, Senator Blunt. And I will turn it over to you.

STATEMENT OF SENATOR ROY BLUNT

Senator BLUNT. Well, thank you, Chair. I appreciate the work we have done together. As you said, this is in my, in all likelihood, last NIH hearing. And as I have started to look back on the time I have spent in the Senate, one of the things I think will have the most long-term impact is what we have done together for NIH research.

You have been a great partner in that effort. We have worked closely with Chairman DeLauro, and Congressman Cole, in the House, who chaired that subcommittee, and they both chaired the committee during the 8 years we have been doing this work together. The entire committee, of course, was involved, but I would particularly like to mention Senator Durbin and former Senator Alexander, who were right there at the beginning of trying to see what we could do to change a trajectory that, really, was not good.

And of course, Dr. Tabak, thank you for you, and the directors being here with us today; and I think all of you would remember when I became chairman nearly 8 years ago, NIH funding was stagnant, and had been for about a decade, but over the past 7 years, working together, we have increased that funding by nearly 50 percent.

It was a period of time that, looking back, the NIH, not only could count on sustained funding, but also having a substantial increase every year. And I am hopeful and confident that Senator Murray's continued partnership in that commitment will let us do that again this year. And I hope we are able to, successfully, work together and have a bill before the end of the year.

I am disappointed that this budget request reduces funding for 12 of the 27 institutes, including the National Cancer Institute, and the National Institute of Allergy and Infectious Diseases. The latter, of course, was demonstrated over and over again how important it was during COVID. There are very few increases, frankly, that are proposed in this request, the increase in CURES is coincidental, and that this fiscal year 2023 year has that number already built in.

The only significant increase, as the Chair has pointed out, at NIH this year, would be an increase of \$4 billion for ARPA-H. Now, I am a supporter of ARPA-H, I am a supporter of the Secretary's decision to have it associated with NIH. But a \$4 billion increase for ARPA-H, and no increase for NIH would really verify

the worst concerns that people have had, about ARPA-H as a competitor to our ongoing research, as opposed to finding a way where the government can and should be willing to take on more financial risks, to become a real partner in targeted research outcomes, that have a specific short-term goal in mind, and to help us reach that goal. That doesn't mean we should jeopardize research challenges as big as cancer, and Alzheimer's disease, or as small as hearing aids, as we look to build, frankly, on the goal of doing more of what we were able to do in the pandemic.

I was also surprised that the budget request failed to take more of the lessons learned from the pandemic into consideration, instead of embracing more high-risk, high-reward science, and focusing on projects with instant impact which proves so successful with programs like RADx (Rapid Acceleration of Diagnostics), it appears that the budget got bogged down with political priorities that don't quite fit the agency's long-standing mission.

This is clearly illustrated with a request for a new Center for Sexual Orientation and Gender Identity, yet virtually no additional money for the Cancer Moonshot. NIH is clearly in a period of transition. If there is one lesson to be learned from the COVID-19 pandemic, it is that our Nation's success depends on medical research infrastructure, across the country, supported by NIH.

Now is not the time to abandon that goal, now is the time, in fact, to make it even stronger. And I hope the original, or the eventual budget that we propose to our colleagues in the Senate, and to the whole Congress, will reflect that determination, to make NIH stronger across the board rather, than the way this budget proposal looks at NIH.

And Chair, thank you for your comments. And thank you for the chance to speak, and for holding this hearing.

[The statement follows:]

PREPARED STATEMENT OF SENATOR ROY BLUNT

Good morning. Thank you, Dr. Tabek and the other Institute Directors, for being here today.

This is my last NIH hearing. As I've started to look back on my Senate career, one of my proudest accomplishments is realigning the priorities within the Labor/HHS bill to focus on medical research.

When I became Chairman nearly 8 years ago, NIH funding was stagnant. And it had been that way for nearly a decade. But over the past 7 years, NIH funding has increased nearly 50 percent, and NIH could count on sustained funding and a substantial increase each year. I am hopeful, with Senator Murray's continued partnership and commitment, we will continue this legacy in my last Labor/HHS bill this year.

I am disappointed, however, that Dr. Tabek has to defend a budget that is nearly indefensible. This is a budget request that reduces funding for 12 of the 27 Institutes, including the National Cancer Institute and the National Institute of Allergy and Infectious Diseases, the latter of which demonstrated its importance during the COVID pandemic. The very few and modest increases that are proposed in the budget request were likely only accomplished because CURES funding significantly increases in fiscal year 2023—a mere coincidence that was not determined by the Administration.

The only significant increase NIH receives this year in the budget request is an increase of \$4 billion for ARPA-H. I am a supporter of ARPA-H and particularly the Secretary's decision to house it within NIH. ARPA-H has the ability to translate what we learned during COVID—that the government can and should be willing to take more financial risks to become a real partner in research outcomes—and expand that model to other research challenges as big as cancer and Alzheimer's disease to as small as hearing aids.

However, no matter how much I support the goal of ARPA-H, it cannot be the sole focus of NIH's budget request. And it cannot displace other scientific priorities or be funded at the expense of other critical research efforts.

I am also surprised that the budget request failed to take more of the lessons learned during the pandemic into consideration to move the agency forward. Instead of embracing more high-risk, high-reward science and focusing on projects with instant impact, which proved so successful with programs like RADx, it appears that the budget got bogged down with political priorities that don't quite fit the agency's longstanding mission. This is clearly illustrated with a request for a new Center for Sexual Orientation and Gender Identity, yet virtually no additional funding for the Cancer Moonshot.

NIH is clearly in a period of transition. The long-time Director has left and we are coming out of a pandemic that has been nearly the sole focus of the agency for the past two-and-a-half years. I hope NIH takes this opportunity to review its current mission and consider whether it aligns with where you want it to be and where you want it to go.

If there is one lesson learned from the COVID-19 pandemic, it is that our nation's success depends on the medical research infrastructure across this country supported by NIH. Now is not the time to abandon it. Now is the time to make it even stronger.

Thank you.

Senator MURRAY. Thank you. I will now introduce our witnesses. We have Dr. Lawrence Tabak, he is the Acting Director of the National Institutes of Health; Dr. Anthony Fauci is the Director of the National Institute of Allergy and Infectious Diseases; Dr. Gary Gibbons is the Director of the National Heart, Lung, and Blood Institute; Dr. Joshua Gordon is the Director of the National Institute of Mental Health; and Dr. Nora Volkow is the Director of the National Institute on Drug Abuse.

Welcome to all of you, and thank you for being here today.

Acting Director Tabak, you may deliver your opening remarks.

SUMMARY STATEMENT OF DR. LAWRENCE TABAK

Dr. TABAK. Thank you, Chair Murray, Ranking Member Blunt, and distinguished subcommittee members. I am honored to be here today with my colleagues representing the NIH. This is a time for NIH and the entire biomedical research community to reexamine all of our efforts. During the COVID-19 pandemic, we were driven by the urgency of the moment.

NIH must learn from this experience, and seize the opportunity to define a new normal. As acting director, I am committed to new strategies, new voices, and a renewed focus on the future.

Now is the time to reflect on what worked and did not work to address COVID and to shape new strategies. Your sustained investment in NIH research set the stage for the new mRNA technology, and immunogen design that were key to the development of safe and effective vaccines in an unprecedented timeline. Since these vaccines became available, it is estimated more than two million American lives were saved, and more than 17 million hospitalizations were averted.

Now we need continued support for a wide range of biomedical fields, including the behavioral and social sciences, to identify and successfully implement better ways of responding to the short- and long-term health effects of COVID-19, to prepare for future pandemics, and to ensure equitable protection of our diverse population.

And it is not just about vaccines. Our Rapid Acceleration of Diagnostics, our RADx Initiative, fueled the development of many

new approaches for COVID–19 testing that are being used in the communities.

To help ensure that such benefits were shared with of those disproportionately affected by the pandemic, we initiated efforts like RADx Underserved Populations, and the NIH Community Engagement Alliance. These experiences, along with other NIH-led efforts focus on COVID treatment development, demonstrate the extraordinary value of public-private partnerships.

The NIH can build upon the momentum of the COVID response, and apply it to other challenges through the Advanced Research Projects Agency for Health, ARPA–H. Thanks to your inclusion of key authorities, and funding in the Omnibus, NIH is beginning to frame the basic administrative infrastructure for ARPA–H. This is a key first step in creating a permanent home for the strategic partnerships that are so urgently needed to address cancer, diabetes, Alzheimer’s, and many other diseases.

But we can’t stop there. In addition to new strategies, biomedical research needs new voices. A growing body of evidence demonstrates that inclusion of diverse perspectives yields better outcomes. In the clinical setting medical teams provide—diverse medical teams provide more accurate diagnoses and improve health for patients while building trust.

We do better science when we have a diversity of scientists, from different backgrounds and communities, scientific fields in various career stages. NIH continues to prioritize, fund and empower early-stage investigators so they can succeed as independent researchers.

In 2021, we reached an all-time high of early-stage investigators, funded 1,513. The passion and commitment of our scientists is matched by the voices of people living with a wide range of diseases and conditions. Conversations with patients and their advocates are sometimes difficult, but those are often the discussions that teach us the most.

From the AIDS (Acquired Immunodeficiency Syndrome) advocacy groups of the 1980s, to today’s groups for autism, ME/CFS (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome), long COVID, and many others, these voices have refused to be ignored, and ultimately, all of us benefit.

This is a moment for renewed focus on the future. I spent a lot of time encouraging early-stage scientists, but I also like to think about the importance of engaging elementary school-aged children, like those my wife has taught, for over 40 years.

During the pandemic, exposure to the importance of science has become a big part of many of their lives. Past pandemics have inspired young people to become scientists, but the images they saw were usually of older men who looked pretty much like me. Hopefully, today’s kids are seeing more scientists who look like them.

Still, we need to do better. Our Nation needs all the bright minds we can find, and I hope you will continue to work with the NIH to make this happen.

Thank you for your time. And my colleagues and I welcome your questions.

[The statement follows:]

PREPARED STATEMENT OF LAWRENCE A. TABAK, D.D.S., PH.D.

Good morning, Chair Murray, Ranking Member Blunt, and distinguished Members of the Subcommittee. I am Lawrence A. Tabak, D.D.S., Ph.D, the Acting Director of the National Institutes of Health (NIH). It is an honor to appear before you today.

I am grateful for the committee's long-standing support for NIH. Whether it is cancer immunotherapy or sickle cell therapies or COVID-19 vaccines, NIH's successes would not have been possible without the investment made by this committee.

The fiscal year 2023 President's Budget will support science that helps tackle many critical national challenges: from initiatives to address health disparities, fight the rising tide of addiction, and transform nutrition science. The budget will also build upon the initial investment in the new Advanced Research Projects Agency for Health (ARPA-H).

ADVANCED RESEARCH PROJECTS AGENCY FOR HEALTH

The President's Request proposes \$5 billion to fully operationalize ARPA-H¹ in fiscal year 2023. This new agency will be a key component to drive transformational innovation in health research and we are grateful for your support. At the direction of the Secretary, we are working to create an ARPA-H that is free to innovate and take risks, an ARPA-H that leverages NIH infrastructure, and an ARPA-H that has unfettered and frequent access to all of the brightest minds across all research fields—from biomedicine to sociology to mathematics. In alignment with the DARPA model, ARPA-H will recruit term limited, visionary program managers who will use its catalytic platform to take on critical challenges in conjunction with traditional and nontraditional partners across academia, government, and industry. ARPA-H will use directive approaches that will provide quick funding decisions to support projects that are results- and use-driven and time-limited, and identify emergent opportunities through advanced systematic horizon scans of academic and industry efforts.

ARPA-H projects would be bounded in time, typically a few years with longer periods allowed for efforts that are highly complex, and with the understanding that a significant fraction of projects will not reach their goals, a necessary outcome when conducting ambitious, innovative research. To determine which bold questions should be undertaken and to evaluate proposed programs and projects, ARPA-H would adopt approaches similar to those utilized by DARPA, such as the "Heilmeier Catechism,"² a set of principles that assesses the challenge, approach, relevance, risk, duration, and metrics of success. It will be critical for ARPA-H to engage with the broader biomedical community, including patients and their caregivers, researchers, industry, community groups, and others, to understand the full range of problems and the practical considerations that need to be addressed for all groups and populations.

CANCER MOONSHOT

The President's Cancer Moonshot^{SM 3} aims to accelerate progress in cancer research and make additional therapies available to more patients. Established in 2016, the Beau Biden Cancer Moonshot was a bold action on behalf of cancer patients. The President's Budget includes \$216 million to the National Cancer Institute for Cancer Moonshot.

Prominent, ongoing Moonshot priorities include immunotherapy, childhood cancer, cancer prevention and early detection, and cancer implementation science. For example, several Moonshot initiatives focus on rare pediatric cancers, including research on the fusion of genes that yield novel "fusion oncoproteins" that drive some childhood cancers. Additionally, Federal agencies, led by NIH, will develop a focused program to expeditiously study and evaluate multicancer detection tests, as we did for COVID-19 diagnostics, which could help detect cancers early, when there may be other, more effective, treatment options for patients. Finally, implementation science strives to maximize the use of proven cancer prevention and early detection strategies and to incorporate them into standards of care, which is an urgent need among underserved, rural, and minority populations.

¹ <https://www.nih.gov/arpa-h>.

² <https://www.darpa.mil/work-with-us/heilmeier-catechism>.

³ <https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative>.

HEALTH DISPARITIES

A key area where NIH hopes to build upon investments made by this committee in fiscal year 2022 is in the agency-wide effort to reduce health disparities. In the wake of a pandemic that disproportionately affected communities of color, this year's President's Budget will enlist most of our Institutes and Centers (ICs) in developing and testing interventions to reduce health disparities that have been appropriately tailored to the breadth of clinical and community services found in diverse settings and contexts.

Importantly, the health disparities research agenda will be aided and informed by the NIH UNITE Initiative,⁴ composed of actively engaged representatives from across all 27 NIH ICs and the Office of the Director. This initiative was launched with the goal of identifying and addressing structural racism within the NIH-supported and the greater biomedical research community through development and implementation of new policies, procedures, and practices. To gain a better understanding of stakeholders' concerns, NIH issued a public Request for Information in March 2021, which captured over 1,100 responses from researchers, external partners, and members of the public. Responses will inform efforts to improve the culture and advance structural change in biomedical research.

NIH has recently launched several more initiatives to improve the health of racial and ethnic minorities and other populations who experience health disparities. One of the funding opportunities will commit \$60 million over the next 5 years to support transformative research to address health disparities and advance health equity.⁵ NIH will also commit \$30 million from 25 Institutes, Centers, and offices to support observational research that will define the role of structural racism and discrimination (SDR) in causing and sustaining health disparities, and intervention research that will address SDR to improve minority health or reduce health disparities.⁶ Finally, NIH will provide approximately \$24 million for the Transformative Research to Address Health Disparities and Advance Health Equity at Minority Serving Institutions initiative, which is designed to support research projects with the strongest potential to have a profound effect on health disparities research.⁷

MENTAL HEALTH

With the fiscal year 2023 President's Budget Request, NIH intends to direct increased attention towards mental health. Mental illnesses are the fifth leading cause of disability in the United States, accounting for 6.6 percent of all disability-adjusted life years in 2019. In addition, suicide rates for youth have risen over the past 2 decades in the United States; in 2019, an estimated 6,488 youth ages 10 to 24 died by suicide. Despite advances in the treatment of depression and other serious mental illnesses, there remain few evidence-based interventions that rapidly reduce suicide risk within healthcare settings. NIH is supporting research projects that focus on testing the safety, efficacy, and feasibility of several of the newest antidepressant interventions—intravenous ketamine and intranasal esketamine (medications known to rapidly reduce depressive symptoms in hours or days) as well as transcranial magnetic stimulation (TMS; a noninvasive treatment that uses magnets to activate specific parts of the brain)—to rapidly reduce suicidal thoughts and behaviors in adults and adolescents.^{8,9}

In response to the pandemic, which exacerbated mental illness throughout the country, NIH launched a project to support research focused on the social, behavioral, and economic impacts of COVID-19, which supports research on the secondary effects of the pandemic, such as financial hardship, reduced access to healthcare, and school closures.¹⁰ The fiscal year 2023 President's Budget requests \$2.2 billion for the National Institute of Mental Health (NIMH), that includes targeted increases of \$25 million to expand research on the impact of the COVID-19 pandemic on mental health, \$5 million to undertake studies of the impact of social media on mental health, and \$5 million to inform mental health treatment ap-

⁴ <https://www.nih.gov/ending-structural-racism/unite>.

⁵ <https://grants.nih.gov/grants/guide/rfa-files/RFA-RM-21-021.html>;
<https://grants.nih.gov/grants/guide/rfa-files/RFA-RM-21-022.html>.

⁶ <https://grants.nih.gov/grants/guide/rfa-files/RFA-MD-21-004.html>.

⁷ <https://grants.nih.gov/grants/guide/rfa-files/RFA-RM-21-022.html>.

⁸ <https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified>.

⁹ <https://www.nimh.nih.gov/news/research-highlights/2021/nimh-addresses-critical-need-for-rapid-acting-interventions-for-severe-suicide-risk>.

¹⁰ <https://covid19.nih.gov/news-and-stories/covid19-ripple-effects>.

proaches, service delivery, and system transformation in support of the Administration's mental health initiatives.

MATERNAL MORBIDITY AND MORTALITY

Even during a global pandemic, NIH has continued to focus on other long-standing yet urgent public health needs. The Centers for Disease Control and Prevention estimates 700 women die each year in the United States of pregnancy-related deaths, 60 percent of which are preventable, and over 50,000 experience severe pregnancy-related morbidity each year.

To address this alarming trend, NIH established the Maternal Morbidity and Mortality Task Force,¹¹ an NIH-wide collaboration. The Task Force coordinates the Implementing a Maternal health and Pregnancy Outcomes Vision for Everyone (IMPROVE) Initiative,¹² which invests in studies to promote an integrated understanding of biological, behavioral, sociocultural, and structural factors that contribute to maternal morbidity and mortality and engages communities in the development of solutions to address the needs of pregnant and postpartum individuals. IMPROVE plans to launch a national network of Maternal Health Research Centers of Excellence that will incorporate local community needs and perspectives to expand and complement existing research efforts by developing, implement and evaluating community tailored interventions to address health disparities in severe maternal morbidity (SMM) and maternal mortality (MM). Through this strategy, IMPROVE will build an evidence-based approach to reducing SMM/MM and its associated health disparities. To support this key initiative, the fiscal year 2023 President's Budget requests \$30 million for IMPROVE. In addition, the request also includes \$3 million for the Eunice Kennedy Shriver National Institute of Child Health and Human Development to support research on mitigating the effects of COVID-19 on pregnancies, lactation, and post-partum health with a focus on individuals from racial and ethnic minority groups.

OPIOIDS AND PAIN RESEARCH

Since early in the pandemic, studies have found increases in the use of many kinds of illicit drugs, including fentanyl, cocaine, heroin, methamphetamine, and cannabis. The NIH Helping to End Addiction Longterm (HEAL) Initiative,¹³ launched in 2018, is a cross-agency program spanning basic, translational, and clinical research on opioid and stimulant misuse and addiction, and pain. HEAL Initiative funds are being used to accelerate the development and availability of longer-acting formulations of existing opioid use disorder (OUD) therapies (e.g., buprenorphine and methadone) and novel immunotherapies (e.g., vaccines) that could block the effect of opioids in the brain to help people with OUD and decrease the incidence of overdose.

The HEAL Initiative is building the Integrative Management of chronic Pain and OUD for Whole Recovery (IMPOWR) network¹⁴ to develop effective treatment interventions for people who experience both chronic pain and OUD. The IMPOWR network consists of clinical research centers that collaborate to develop effective interventions, best models of care for delivery of services, and sustainable implementation strategies for a variety of patients with co-occurring chronic pain and OUD or opioid misuse, with an emphasis on highly vulnerable groups.

In 2020, this committee directed NIH to expand HEAL to address methamphetamine use and we are making progress toward this goal. For example, NIH-funded research on immunotherapies for stimulant use disorders led to the development of a monoclonal antibody called IXT-m200 that targets methamphetamine.¹⁵ This treatment has received Fast Track designation from the Food and Drug Administration and is now being studied in emergency department settings in people with methamphetamine overdose.¹⁶ It is the first novel, investigational treatment for methamphetamine addiction ever to advance in the medication development process to a Phase 2 clinical trial. In order to continue to respond to these evolving chal-

¹¹ <https://www.nih.gov/research-training/medical-research-initiatives/improve-initiative/trans-nih>.

¹² <https://www.nih.gov/research-training/medical-research-initiatives/improve-initiative>.

¹³ <https://heal.nih.gov/>.

¹⁴ <https://heal.nih.gov/research/clinical-research/integrative-management-chronic-pain>.

¹⁵ <https://nida.nih.gov/news-events/nida-notes/2020/02/part-2-immunotherapies-new-tool-to-treat-methamphetamine-addiction>.

¹⁶ <http://intervexion.com/2016/01/intervexion-therapeutics-announces-fast-track-designation-of-ixt-m200-for-treatment-of-methamphetamine-addiction/>.

lenges, the fiscal year 2023 President's Budget includes total funding of \$2.6 billion in this research area across NIH's ICs.

Importantly, NIH seeks to involve many more of our ICs in this initiative, particularly with respect to research addressing pain. The fiscal year 2023 President's Budget Request will expand research into effective therapies that don't involve the brain or the central nervous system by involving researchers from many Institutes and Centers like the National Institute on Dental and Craniofacial Research (NIDCR),¹⁷ which I led for a decade prior to becoming the Principal Deputy Director of NIH. As a dentist, I know that there is no group of clinicians who have more to contribute or more to gain from identifying better pain management approaches. For example, researchers have identified clinical signs and symptoms that can help predict whether temporomandibular disorder pain will linger and turn into chronic pain. Research at the National Center on Complementary and Integrative Health¹⁸ proposes to investigate the role of the brain in pain processing and control, and how factors such as emotion, attention, environment, and genetics affect pain perception.

NUTRITION RESEARCH

The complexity of human nutrition, combined with the impact of diet on chronic diseases that were a contributing factor to the excess deaths of the pandemic, demands that cutting-edge data science and system science methods be employed to move nutrition science into the 21st century. To reflect the high priority NIH places on innovative, multidisciplinary nutrition research, in 2021 the NIH Director moved the Office of Nutrition Research (ONR)¹⁹ to the Office of the Director. Dedicated funding is critical to ensure that the ONR can operate effectively as a cross-cutting NIH entity and to accomplish the goals of the plan. The fiscal year 2023 President's Budget requests \$97.2 million for the NIH Office of the Director to support ONR.²⁰

Within this amount, one new collaborative project proposed is Reducing Nutrition Health Disparities through Food Insecurity and Neighborhood Food Environment Research. This research will use precision regional implementation science and pragmatic research approaches to test strategies to ensure food security and access to healthy food, which are intended to prevent disparities in a variety of diet-related diseases and conditions, such as cardiovascular disease, obesity, diabetes, and cancer. Elucidating the role of these social conditions on diet and nutritional status could help address and prevent diet-related health disparities and promote health equity.

This kind of population and system science will be an important complement to the Nutrition for Precision Health program²¹ (awarded in January 2022 to recruit 10,000 diverse participants to study how a person's nutritional status, metabolism, microbiome, genetics, and environment affect health) and the \$50 million Artificial Intelligence for Chronic Disease initiative (first funded in fiscal year 2021, the initiative leverages machine learning and data science tools to untangle the complex underlying causes of chronic diseases and look for early treatments).

NIH BUILDINGS AND FACILITIES

NIH strives to ensure that its facilities are safe and enable scientists to discover new diagnostics, therapies, and cures. As part of this effort, the President's Budget proposes \$300 million for NIH's Buildings and Facilities appropriation. These funds are meant to begin addressing the backlog of life and safety repairs that totaled over \$1 billion in the 2019 report by the National Academies of Science, Engineering and Medicine on the condition of NIH's facilities on the Bethesda Campus. A key aspect of NIH's strategy is to sustain the condition of existing facilities to prevent premature deterioration and the curtailment of research, including the physical plant, building structures, utility systems, roads, and grounds at all NIH sites. These projects will help to ensure the continued efficient and effective performance of NIH's real property assets to meet ongoing and projected research requirements and to offset the deterioration and obsolescence caused by age and use.

The President's Budget request also proposes a modification to the language governing repairs, which is intended to move NIH's property stewardship beyond maintenance and repairs to more proactive efforts like the modernization at NIH's re-

¹⁷ <https://www.nidcr.nih.gov/>.

¹⁸ <https://www.nccih.nih.gov/>.

¹⁹ <https://dpcpsi.nih.gov/onr>.

²⁰ <https://officeofbudget.od.nih.gov/pdfs/fiscalyear23/ics/27%20-OD%20FY%202023%20CJ%20Chapter.pdf>.

²¹ <https://commonfund.nih.gov/nutritionforprecisionhealth#:~:text=The%20goal%20of%20the%20NIH,prevention%20and%20treatment%20of%20disease>.

search hospital, replacement of obsolete, temporary, and fragmented research facilities, improvement of facilities that advance computational and data science, and improvement of the energy and water efficiency of buildings. To achieve this will take time, so NIH looks to leverage prioritization processes currently in place to focus on the projects that are of the most need to our organization.

CONCLUSION

A healthier nation is a more productive nation and a vibrant research community is a pillar of an economically sound nation. With your support, NIH looks forward in fiscal year 2023 to continue the tradition of catalyzing major break throughs over decades, bettering the human condition through rigorous and innovative science. My colleagues and I look forward to answering your questions.

Senator MURRAY. Thank you very much. And I realized it as I was going through the list of panelists in front of us, I skipped Dr. Richard Hodes, is the Director of National Institute on Aging. Welcome to you as well.

We will now begin a round of 5-minute questions of our witnesses, and I ask my colleagues to please keep track of the clock and stay within your 5 minutes.

DRUG OVERDOSE

Dr. Volkow, I want to start with you. As I mentioned in my opening remarks, across the country overdose deaths continue to rise dramatically. Last year they spiked in my home State of Washington by 30 percent, and much like the rest of the country, were really driven by fentanyl.

This is really a national crisis, so we have got to be using every tool that we have to support our communities, including fentanyl strips, which Secretary Becerra mentioned at his hearing here a few weeks ago. The research I have seen indicates that those strips which are used to detect fentanyl in drugs, are an effective overdose prevention tool, but they require several steps to use them, including chipping off some of the pill to be able to test it.

Can you tell us what the research shows about the effectiveness of those test strips? And really, are they easy to use? Can you talk a little bit about that?

Dr. VOLKOW. Thanks very much for that question. And indeed the fentanyl test strips have been tested for sensitivity and specificity, and the data shows, actually, high sensitivity, and there are only a few fentanyl analogs that are not detected.

Having said that, the fentanyl test strips were developed for testing drug use in urine, so for patients that are being monitored; and so now this is a new application, and as a result of that there can be problems on how it is implemented.

Overall, patients that have used the fentanyl test strips report positive outcomes, and actually in terms of identifying drugs that may put them at higher risk. The research is now ongoing to try to determine what are the optimal guidelines on how to use them, number one; but number two, if the results were positive, what is it that an individual should do in case that they still want to consume them.

As you know there are still multiple problems in terms of making these fentanyl tests available throughout the United States, and there is interest on actually determining and getting approvals for some of these tests by the Food and Drug Administration, so they

can be utilized in healthcare settings, which is not possible at this moment.

OVERDOSE PREVENTION

Senator MURRAY. Well, are there overdose prevention strategies that you and HHS (Department of Health and Human Services) hope to roll out in the coming months? Talk to me a little bit about what we are doing in terms of prevention.

Dr. VOLKOW. Prevention strategies that have been shown to be widely effective is perhaps one of the most important ones, is widespread distribution of Naloxone, and that becomes actually, in some instances, a challenge if the Naloxone is not available for those that use them.

Another harm-reduction practice that has generated a lot of attention, is the extent to which, because the drug supply is so extremely dangerous these days, in which safe injection sites could be viable for patients that otherwise may be at high risk of overdosing. And while the data is still preliminary in the United States, in other countries they have shown that in certain settings they can be quite effective. So there is interest on evaluating them.

There is also interest in the community to test other products that may serve as harm reduction, for example, the use of kratom, which is sold as tea, and that contains a drug—a molecule that has the effects that are similar to those of buprenorphine, but could be utilized also for decreasing withdrawal or depression. So these are more novel, and we don't have sufficient data, but those are things that are being discussed.

ALZHEIMER'S DISEASE

Senator MURRAY. Okay. Thank you.

Dr. Hodes, it is said that science is a marathon, not a sprint. However, Congress has really approached investing in research to treat and cure Alzheimer's disease and related dementias, with really a sense of urgency. We have poured resources into this research, \$17 billion since 2015 to really supercharge the discovery process with a goal of finding a treatment or cure by 2025.

And I am concerned that NIH isn't positioned to meet that deadline. Given the sheer scale of Federal investment, what is NIH doing to deliver meaningful and measurable outcomes that assess its progress towards finding effective treatments?

Dr. HODES. Thank you for that critical question. And let me answer it very briefly in terms of process, and then with some examples of meaningful accomplishments during this time. As you know, we have counted on critical input from the national and global research communities, advocates, et cetera, with our annual summits, all of which feed into a careful identification of milestones, that is the goals and targets which are necessary to meet our most important needs.

I want to take a moment just to thank the staff of this committee for the interactions we have had over the past year to help us focusing these milestones into meaningful, quantifiable outcomes, and making them transparent and available.

To touch on just some of the examples of the important advances, I would point starting with our clinical trials. So for example, in

pharmacological trials, there are currently eight studies targeting amyloid, or not, which are Phase 3, in their latest stages capable of identifying definitive, positive outcomes, meaningful outcomes, clinically which are due over the next years to reveal their answers.

There are some 62 early-phase clinical trials, and a variety of targets, three-fourths of them not amyloid, and these are the results of basic science, which has found more and more potential targets. So the clinical trials, or investment in them, are critically important, and you alluded as well, to the burden on the families, and those living with dementia, that is also an area of clinical research, clinical trials, And we now are funding a large number of trials studying interventions for care and care providing, which will be producing their results.

The National Academy has identified two of those generated with NIH funds that are ready for dissemination, being disseminated with further evidence. Happy to elaborate as time allows, but these are some of the examples of accomplishments, and of our important process to continue being accountable to ourselves, to you, and to the public for making the best use of these very critical funds to accomplish the highest of the priorities.

Senator MURRAY. Well, thank you. And I think transparency is really important. The deadline is around the corner, and we have put out a lot of money for this, and need to know, as Congress, how those investments are going.

So I look forward to working with you. And Senator Blunt will look forward to working with you on that as well.

Senator BLUNT. Thank you, Chair.

UNDIAGNOSED DISEASE NETWORK

Dr. Tabak, during the time you were Deputy Director, the seven hearings we had with Dr. Collins, who was the Director at the time, I think every single time he talked about the importance of NIH bringing hope to millions. I want to talk a little bit about the proposed ending of funding for the Undiagnosed Diseases Network.

We have one of those in St. Louis; Chair Murray has one in Seattle. I had somebody reach out to me a couple of weeks ago, Michele Herndon, from Affton, Missouri. She was concerned because her son, Mitchell, who had suffered from a series of health issues that doctors couldn't diagnose, had benefitted from one of the centers.

In fact, by late-high school, he was in a wheelchair, his hearing was gone, and his eyesight was gone. They were losing hope, but after they sought treatment at the Undiagnosed Disease Network in St. Louis, they found a neurological condition so rare, that it didn't even have a name.

In fact, Mitchell lost his battle. The condition he had now carries his name, the Mitchell syndrome. But Michele and her family were comforted by the fact that they finally knew what this long struggle had been about. This year's budget cuts the Undiagnosed Diseases Network, and closes all 12 of its clinical sites.

She was concerned about that. I am too. I think there is some discussion where they may graduate in some way to where they continue to exist. I think it would be a problem to walk away from

that. Not everybody can come to NIH in Bethesda. And if you don't have the site within some reasonable distance of where you are, you are unlikely to get this service. Do you want to talk about why that decision was made to stop funding these 12 sites?

Dr. TABAK. We certainly agree that the diagnostic services provided by the Undiagnosed Diseases Network are extremely valuable to patients and to their families. The challenge that we face is there does come a point where the diagnoses become a part of standard care, versus a research question, but finding that right balance is something that we continue to work through.

All the cases that are enrolled presently will continue to undergo comprehensive evaluation. We will establish a Data Management and Coordinating Center to draw upon the experience of all of the centers that are participating in this program. But really, we would like to work with you, going forward, to come up, perhaps, with a better solution in the mid- and long-term.

Senator BLUNT. Good. Well, let us continue to work on that. I mean, really you can't have standard care if you are still discovering things that needs to be looked at as an option. Mitchell syndrome is Mitchell syndrome only because he was the first, and may be the only diagnosed person so far, that ever had that. And that is going to fall outside of standard care definition, I think. So let us continue to work on that.

RADX

Is Dr. Gordon available? Let me ask him, on RADx, Dr. Gordon, in the mental health area, and in the RADx example of, again, NIH itself, partnering directly with others to try to find a rapid solution. Do you think that a Shark Tank RADx kind of option would be a possibility, as you look for biomarkers in mental health?

Dr. GORDON. I think that is a great idea, Senator Blunt. I appreciate your support of that initiative, and NIMH (National Institute of Mental Health) as well. We have funded a number of small businesses, as well as a number of academics, who have come up with really wonderful ideas for biomarkers that can help guide clinical decisionmaking. Something that we desperately need in psychiatry to help speed treatments and make sure the people who need treatment, get the right treatment from the get-go.

And one of the ideas for it, we have been thinking about is using the RADx example where you had, essentially, a competition between a number of different companies in RADx, it was for tests for COVID. But the idea is to apply something like that to the biomarker space for mental health.

And we think now is the right time to do that, and so we are talking with our colleagues at NIBIB (National Institute of Biomedical Imaging and Bioengineering), who ran the RADx competition, and trying to figure out how we can do that for biomarkers for mental health.

Senator BLUNT. Very good. I would encourage that. I think every single home test for COVID comes out of the RADx experience, and again, if you have got people that have ideas that can come to you, and see which of those you should partner with; I think that would be a great step in the right direction.

Thank you, Chair.

Senator MURRAY. Senator Reed.
 Senator REED. Thank you, Madam Chairman.

SUICIDE

Dr. Gordon, we are in the midst of a significant spike in suicides, particularly among children, which is very disturbing, and we know some of that is a result of the pandemic, but I am just interested in what research at NIH is pursuing this issue, to recognize warning signs. How is that research being operationalized, and put out to practitioners, particularly, and to families? And then the other point would be, we have a new national hotline, 988, are you in any way, sort of trying to coordinate, or work with that, or study that?

Dr. GORDON. The answer to both those questions is, yes, we are deeply involved in making sure that our research informs practitioners both in the clinic and at the State level when we are talking about 988.

Let us talk about youth suicide first. NIMH has funded a number of research programs in identifying individuals at risk, particularly the young, and in getting to evidence-based care. One quick example, the NIMH Intramural Program developed a screening questionnaire called the ASQ (Ask Suicide-Screening Questions) that has been disseminated to primary care practices, and pediatric emergency rooms throughout the country, and really it is being used nationwide.

We also have funded a number of research projects, looking at school-based identification and prevention measures as well, and we do our best to make sure that they are out there.

We also work with Federal partners, like the Substance Abuse and Mental Health Services Administration, or SAMHSA, and there we are working with them, especially around the 988, looking, to try to make sure that States that are implementing the follow-ups to 988, are aware of evidence-based approaches to mental health crises.

For example, the proper utilization of mobile crisis teams that are trained in responding to individuals in mental health crises is one evidence-based approach that has been proven over and over again to work. So yes, and we continue to work in both of those areas. Thank you.

Senator REED. All right. Thank you, Dr. Gordon.

LONG HAUL COVID

Dr. Fauci, the issue of long-haul COVID has been dominating the news lately. Can you describe how NIH is tracking these cases? Are there common elements to them? Are there treatments showing any promise? Where are we in the process of tackling?

Dr. FAUCI. Yes. Thank you very much for that question, Senator. I will begin the answer, and then I will hand it over to Dr. Gibbons, who is also very much involved in this.

Senator REED. Thank you.

Dr. FAUCI. As you well know, this is a real phenomenon, and the epidemiology of it is still being worked out, I mean, the range of people anywhere from 5 percent to up to 30 percent of people have

the persistence of symptoms that are not thoroughly explainable by any pathogenic process that we have been able to identify.

We put together large cohorts that are now being followed, both to understand the actual prevalence, incidence, as well as the pathogenesis.

With regards to treatment, Senator, it is very difficult to do any treatment for it when you don't know exactly what the pathogenic mechanisms are, and that is the reason why we are putting so much effort into trying to find out just what is going on. Is it immune activation? Is it persistence of virus? Not necessarily replication competent virus, but maybe particles of virus such as the nucleotides.

But let me hand it over to Dr. Gibbons who could also tell you a bit about that.

Senator REED. Thank you.

Dr. GIBBONS. You know, I only add to Dr. Fauci's comments, that we are indeed setting up the recovery—researching COVID to enhance recovery effort. It is moving with a great sense of urgency given the suffering of the patients with long COVID. There are a number of elements that have launched effectively. One is to create an electronic health record, a base set of cohorts. They are derived from 60 million records of patients across the country.

A diverse body of patients, of which, between four and five million have COVID, and that provides an opportunity to track those individuals electronically, and digitally, and longitudinally, to see who develops long COVID, who does not, that can inform, as Dr. Fauci mentioned, our understanding of the prevalence, as well as the risk factors, as well as the long-term effects, chronically.

It is already starting to show preliminary evidence that is suggestive of—potentially the ability of vaccination to prevent the development of long COVID. Similarly, they were seeing signals that are telling us that the severity on the acute COVID has bearing on your susceptibility to develop long COVID.

Similarly, we are seeing trends towards, who is most affected. And again it is identifying people of color, African-Americans and Latinos as a high-prevalence group, developing long COVID that really hasn't come to the fore as much; and so we are learning as we go and develop this program. Thank you.

CHILDHOOD CANCER STAR ACT

Senator REED. Thank you very much. Just a final point, if I may. We have to reauthorize the STAR (Childhood Cancer Survivorship, Treatment, Access, and Research) Act. It is the best thing we have done in a long time, with respect to childhood cancer.

And I think you would agree, Dr. Tabak? Just a nod of the head is sufficient.

Dr. TABAK. Yes.

Senator REED. Thank you. Thank you, Madam Chair.

Senator MURRAY. Senator Kennedy.

Senator KENNEDY. Thank you, Madam Chair.

Dr. Tabak, what the National Institutes of Health has done, and continues to do is nothing short of extraordinary, I mean, it is really breathtaking. And I want to thank you and your colleagues for doing that.

We have all been to pandemic school for the last several years, and I want to use the few minutes I have to explore what we have learned.

COVID RELATED SCHOOL CLOSURES

Dr. Fauci, whether you asked for it or not, you have sort of been the government's face on the response to the pandemic. Looking back, and I recognize that hindsight is crystal clear, but looking back, do you think it was worth it, do you think the benefits were greater than the costs of closing down our elementary and secondary schools?

Dr. FAUCI. I think it is difficult to give a definitive answer to that. I know in the very beginning when we had really no other protection prior to vaccinations that were available to contain, somewhat, the spread of the virus. One of the things that was felt to be important would be to protect children as well as the rest of the population.

Right now we have felt, more than just recently, that it is very important to keep the children in school for the simple reason that we know of the deleterious effects, both psychologically, mentally, and developmentally in children, to keep them out of school. But you have to have a delicate balance between protecting the children from getting infected, and perhaps bringing the——

Senator KENNEDY. Did we strike the proper balance?

Dr. FAUCI. You know, I believe that we have. It is very tough to tell. I think only time will tell whether that is the case, because there is indication that has been deleterious effects on children, but we believe from a public health standpoint, that at the time it was the right decision.

Senator KENNEDY. Well, can I ask you this Doctor. And I realize, I am not asking—I am not saying, or offering judgment of what was done at the time. I am asking what we have learned. Let us suppose we have a substantial increase in prevalence of the coronavirus next week, God forbid.

Dr. FAUCI. Right.

Senator KENNEDY. Would CDC (Centers for Disease Control and Prevention) recommend shutting down the elementary and secondary schools?

Dr. FAUCI. It is very difficult for me to speak for the CDC, but knowing the fact that we——

Senator KENNEDY. Would you recommend it?

Dr. FAUCI. Right now, I would do everything we can to keep the children in school, and not shut down the school. And that has always been my strong recommendation, to the extent possible, not to keep the children out of school.

Senator KENNEDY. But yet we did shut down.

Dr. FAUCI. But to keep them safely in school, by getting children that are available to be vaccinated, vaccinated.

Senator KENNEDY. Right.

Dr. FAUCI. To get the children who are eligible to be boosted, vaccinated, and to surround the children with teachers and personnel in the schools who are vaccinated. That is the best way to protect the children while keeping them in school.

Senator KENNEDY. Okay. Let me ask you this. In hindsight, knowing what you know now, had you known it then, did we do the right thing in shutting down society? Would we have been better off saying: No, we are going to protect the vulnerable, the elderly, the people who are immunocompromised, and we are going to isolate them but have the rest of American society, churches, businesses, universities, schools go on about their business, while at the same time providing them guidance about how to protect themselves?

Dr. FAUCI. Well, it is a complicated question, I will try and give as simple an answer as possible. I think there is a misperception about who the vulnerable are. There are many, many more vulnerables in society, and there is a misperception that the only vulnerables—

Senator KENNEDY. Yes. But I am about to run out of time. Let us assume we can agree on a definition.

Dr. FAUCI. I don't think you can. I think that society is very heterogeneous, and it isn't a question of shutting down completely, Senator, because we never shut down completely. If you do shut down a society you do it for a purpose, and the purpose is, at that period of time when you are protecting people from interaction, that you get as many people vaccinated as you possibly can.

Senator KENNEDY. Let me stop you at that.

Dr. FAUCI. To shut down—

Senator KENNEDY. I am going to run out of time. Let me ask you one last question.

Dr. FAUCI. Sure.

Senator KENNEDY. What would you do differently today?

Dr. FAUCI. Right now I would hope that we would get many more people vaccinated.

Senator KENNEDY. No. But what would you do when you did it, in hindsight, if you knew then what you know today?

Dr. FAUCI. It depends on when we got the vaccine. Do you mean before the availability of vaccine? Before the availability of vaccine, when we had no other situation, I would try to protect people by making sure that they masked, and kept themselves separated from this congregate, indoor settings, that is what I would do, in the absence of a vaccine.

But right now I think it is important, looking forward, we still only have 66 percent of the total population vaccinated, and less than half of those are boosted. I think we can approach what we are likely going to be seeing, and are seeing now, with an increase in surges, with the possibility of a surge in the fall and winter.

One of the real things we can all do as a Nation, is pull together and try to get our people vaccinated, and those who are eligible to be boosted, boosted. That would solve a lot of the problems that you are referring to.

Senator KENNEDY. Okay. Thank you. Thank you all.

Senator MURRAY. Thank you. Senator Baldwin.

Senator BALDWIN. Thank you, Madam Chair.

SUBSTANCE ABUSE EPIDEMIC

Welcome, Dr. Tabak. I am posing the first question to you for an update on research efforts to better respond to the substance-use

epidemic, by way of context. As you well know, the substance-use epidemic continues to ravage communities across Wisconsin, and across the United States, and an increasingly dangerous role is played by synthetic opioids, such as fentanyl, as well as psychostimulants, like methamphetamine.

So I believe it is vital that we invest in sustained research into substance-use disorders to prevent deaths, treat patients, and make our communities safer. If you could describe recent research efforts, including what is happening with the HEAL Initiative, the Helping to End Addiction Long-Term Initiative, I would appreciate that.

Dr. TABAK. If I may, to turn to Dr. Volkow, who is our expert in this field.

Senator BALDWIN. Absolutely.

Dr. VOLKOW. Thanks very much for the question. And our research is actually going from the basic to help develop medications with new targets, to help develop formulations that can be—actually lead to better outcomes. To epidemiology research to understand the changing face of the overdose crisis, which now, as you are mentioning, is no longer just limited by our overdoses from prescription opioids, but encompasses overdoses from fentanyl, methamphetamine, and cocaine, to the implementation research that can help us determine what are the optimal models of care that we can deploy in community, and to take advantage of infrastructure.

So for example, research is ongoing to determine how the health care system can be involved in the prevention and treatment of substance-use disorders, and how can we bring treatments to justice settings, like prisons, and jails, and upon release, and maximize the possibility of these individuals to get healthcare, to the involvement of community, so that we can actually integrate the effort between healthcare, justice, and communities.

Through the HEAL Initiative, we have been able to accelerate significantly. Also, another area that has been neglected, overall, which is the need to better treatments for the management of severe pain, and if we do not address the need of patients suffering from severe pain, we keep them as very, very vulnerable, to seeking out much more dangerous drugs, out in the illicit market.

And finally, we need to also ask ourselves: What is it in the United States that is making Americans so vulnerable to the use of these drugs? And that is relevant to prevention, because if we do not understand it, then we cannot do interventions to actually protect those that because of circumstances alien to them, are actually at much higher risk to taking drugs, and ultimately develop addiction or overdosing.

Senator BALDWIN. I appreciate your response.

INVESTMENT IN RESEARCH

Dr. Fauci, the U.S. was able to bring a COVID-19 vaccine to the public in really record time. And I am grateful for the work of so many that made that possible; including several who are in this room.

Unfortunately, the next pandemic, driven by an unknown disease X will come. And I believe we can't wait. We should invest in the development of novel antivirals, and vaccines, and diagnostics for

unknown threats from priority viral families, now, so that we are better prepared in the future.

Can you explain how the investments we have made over time at NIH and across the Federal Government, made the COVID-19 vaccines and medical countermeasures possible? And how would sustained investments to develop responses to viral families of concern make us better prepared?

Dr. FAUCI. All right. Thank you very much for that question, Senator. Yes, it is very, very clear that the investment in basic and clinical biomedical research for at least a few decades, and maybe more, prior to the realization that we are dealing with a new, historic pandemic, allowed us to do something that was completely unprecedented.

Two examples of that are the work that was done on what we call vaccine platforms, the mRNA vaccine which was fundamental, basic research, on how to get the mRNA molecule to actually serve as a platform for vaccine.

Work at the NIH, in our own campus, as well as NIH-funded investigators throughout the world, also worked on what is called immunogen design to do work that led to the ability to stabilize the optimal immunogen, in this case it was the spike protein, which allowed us to go from the realization of a new pathogen, on January 9-10, 2020, getting into Phase 1 trial, in 65 days and 11 months data, having a safe and effective vaccine.

We did that because of the investment you are referring to. Right now, looking forward, we have what is called a Prototype Pandemic Preparedness Plan, which means you do just what I believe you are alluding to. You develop a number of families. There are about 20 families that are the high risk, of those there are about 7 families of viruses that if you do the fundamental work of looking at the commonalities among them, and develop diagnostic tests, assays, immune correlates, and do that now.

And if we don't get the resources now, Congress has been very generous to us up to now, but if we don't get the resources we need, we are not going to be able to do the kind of preparedness, not only for vaccine, but also for targeted development of antivirals, which we did so successfully with HIV (human immunodeficiency virus), and did quite successfully right now.

But we have programs that are not going to get off the ground unless we get funding. So fundamental basic, and clinical research are the core of everything that is going to protect us in the future. Thank you.

Senator MURRAY. Senator Braun.

FUTURE COVID LOCKDOWNS

Senator BRAUN. Thank you, Madam Chair. So I am going to have two questions, and I would like Dr. Tabak and Dr. Fauci to answer each of the two questions. I am going to start with this one.

So in navigating through the entirety of what we did to fight COVID, clearly, the most expensive feature of the navigation would have been lockdowns. We did that out of uncertainty, we had no idea, you know, how that was going to work.

Even in the business I ran, you had early dust ups, where you would get a case and clear out a warehouse. And we quickly under-

stood you do not throw caution to the wind, and you take the basic information that we all had to deal with, and you took it seriously, you put protocols in.

Let us look at lockdowns. It costed us trillions of dollars, and we are paying for that now, with super-high inflation. You know, I think I am interested in, when Johns Hopkins comes out with a study that said basically that didn't have any impact on mortality, and I don't know that that study addressed what mortality might have been impacted, in terms of deferring other healthcare. Can we take lockdowns off the table in terms of what we do in the future? Dr. Tabak, and then Dr. Fauci.

Dr. TABAK. I can't say, because I don't know what that future holds for us. If you have a pathogen that is very virulent, very infectious—

Senator BRAUN. Let us assume it is in the same modality as what we have been navigating through over the last couple 3 years.

Dr. TABAK. I think the initial presentation of the virus was one that was devastating. It killed a lot of people.

Senator BRAUN. What about the study that Johns Hopkins did, because we are always saying, pay attention to the science?

Dr. TABAK. I am not familiar with that study, sir.

Senator BRAUN. Dr. Fauci.

Dr. FAUCI. Senator that is a very good question. If you are going to lock down, you have got to use it temporarily for a reason to prepare you to be able to un-lock down, and get the public prepared for that.

Right now, looking forward, I don't see the need of lockdown in the future unless something really, very, very unusual happens. And the reason is, that what we really need to do, is we need to get our population vaccinated, and we need to get them boosted. That would completely obviate the need to lock anything down.

So right now if you ask me the question, looking forward, do I see, even if we do get a new variant, I think the vaccinations that we have, have enough cross-reactivity and our ability, with proper resources, to make variant-specific boosts, I don't see lockdown in the future. Lockdown is a temporary thing, to get you to be able to move quickly to save lives.

Senator BRAUN. That is good to hear, because in that kind of moment of uncertainty, I don't think we could afford to do it again. I hope the Biden administration is listening to that.

VACCINE MANDATES

The other question; and I led the effort on it; is when we took this and distilled it down to, you either get a vaccine or you lose your job. And thank goodness, we did marshal bipartisan support that said that didn't make sense, Supreme Court used that as a cue, you know, in terms of what they did to abrogate that.

So in the future, will we heed what the Supreme Court said, and that you wouldn't calculate, even though don't disagree that vaccines are an important tool, along with therapeutics, and preventative? Would you push to do the same thing that we almost did, that would have been the second calamity to occur? In terms of what it would have cost the economy, and probably not benefit from a result that would have been measurable?

Dr. Tabak, and then Dr. Fauci.

Dr. TABAK. As you know the vaccination is the single most effective preventive measure, and so to the extent that the law allows, you would want to continue to act——

Senator BRAUN. But would you recommend that we go down that path again, down to 100 employees in a business, to where you said, either get it, or lose your job.

Dr. TABAK. That is a policy call, sir. I don't make those calls.

Senator BRAUN. Dr. Fauci.

Dr. FAUCI. Again, it is a policy call. I would hope that we would marshal everybody, you know, both sides of the aisle, to get out there and encourage everybody to get vaccinated, and if they did, we wouldn't even have to address that question. I don't like mandating things. I don't like punishing people for not doing something.

But I would hope that they would realize, if you look at the data, and you just made an appropriate statement, Senator, a moment ago, about following the science; if you look at the data, of the differences in vaccinated versus unvaccinated people, and hospitalizations, and death, it is striking what it is.

So as a public health person, I would say why don't we all pull together to get people vaccinated. We won't have to worry about, essentially, putting what appears to be and is in fact a penalty if you don't.

Senator BRAUN. And I think the key to that navigation is to pay attention to the data, and the science, not the political science.

Dr. FAUCI. Right, exactly.

Senator BRAUN. Thank you.

Dr. FAUCI. Thank you.

Senator MURRAY. Thank you. Senator Rubio.

Senator RUBIO. Thank you. Thank you all, for being here.

GENDER TRANSFORMING CARE

Dr. Tabak, let me start with this question. You know, we have recently seen that the—not just the Biden administration, but the Biden administration, and others in the policy realm, have been actively promoting and supporting the use of things like, puberty blockers, and hormone therapy for young boys and girls. I want to sort of limit my question to minors, for what they have termed gender transforming care.

That is not an FDA-approved use of puberty blockers and hormone therapy I don't believe in any people, but especially in minors. So as the NIH is America's medical research agency, what work have we done at NIH, what work has been done to determine if this non-FDA-approved use of these medicines, this off-label use of these medicines is appropriate for minors seeking gender transforming care?

Dr. TABAK. So NIH funds a small number of observational studies to gather the data on the effects of treatments that transgender youth and their parents have chosen. And there are also a small number of studies that describe the health issues and risks, including HIV that are unique to these transgender youth. But all of the research in this space is observational. We do no interventional work.

Senator RUBIO. I guess, my question is before—one thing is a decision made by an adult, right, and especially given the irreversible nature of some of these treatments, isn't there some wisdom in the notion that before policymakers are out there promoting the off-label use of medications that lead to permanent changes, that there be some more research done on its impact, you know, 5, 10, 15, 20 years from now?

Dr. TABAK. So as you know, transgender youth are more vulnerable to depression, anxiety, engaging in self harm, and so it is important that we examine and evaluate the potential effects of these treatments.

Researchers are observing longer term psychological impact of these protocols, and so by looking at individuals, transgender youth, with and without histories of puberty suppression, we will be able to better answer the types of questions that you are posing.

Senator RUBIO. Yes. I guess my—that is my point. My point is, we don't know what its long-term implications are when we weight the costs and the benefits. The FDA (Food and Drug Administration) hasn't approved this, and yet we have policymakers promoting it. And I think that is an important point.

I mean, clearly, we don't want anybody harming themselves, and things of this nature, but we don't know what—these policy decisions are being made on the basis of observational guidance, and by your own admission, without any sort of long-term trajectory on its holistic impact.

COVID TRAVEL RESTRICTIONS

Dr. Fauci, I am running into something that is pretty interesting. I believe the United States is the only major Western country that now requires its citizens to test negative for COVID before they can get on an airplane and reenter the country. I believe that is accurate.

And on the other hand, we are hearing now that, for example, Title 42, which is a COVID-era policy should be lifted because we have reached the point now where COVID is manageable, or at a level where we no longer need Title 42. And we obviously know we have a problem in our southern border where every day people are entering the country, illegally, and many are not even being tested for COVID. And even if they are, they are being allowed to stay, and most certainly would under Title 42.

I don't understand. How do we tell American citizens, if you test positive, even if it is a dead virus that has been in your system for 10 days, because you can test positive days after you are no longer infectious, and you can't enter your own country? But people—if you arrive illegally, whether you test positive or not, if you say the magic words for “asylum” you get to stay in the country.

And this is a real-life scenario. I know people that are abroad, they test positive, they are not sick; maybe they were sick a week ago. And they can't afford to continue to pay for hotel rooms, and staying overseas until they can finally score a negative test.

Has the time come for us to lift this, in your view; you know, having been so integral in our COVID response? Are we at a point now where American citizens should be allowed to return to their country without testing negative?

Dr. FAUCI. You know, I am not—thank you for the question. It is an important question. I don't have the answer to that. I mean, we work with our CDC colleagues to continue to examine the feasibility of that, and the desirability of that. I think the idea of having an immigration issue mixed with a public health issue for the general population; I think those probably should be separated.

Senator RUBIO. Well, except they are interrelated, because they both involve groups of people entering the United States. One group is citizens of the country entering legally, the other group, frankly, are people that are not entering legally. The group that is not entering legally, even if they test positive, if they are even tested, get to stay; the American citizen can't reenter their own country until they produce a negative test.

And my point is, if we have reached the point in COVID, where we no longer need Title 42 as a COVID restriction for illegal entry, why do we still need travel restrictions for American citizens for legal entry into their own country? That is the genesis of the question. That is where I think the link is the—it sort of seems to be at odds with it.

Dr. FAUCI. Yes.

Senator RUBIO. All right. Thank you.

UNIVERSAL COVID VACCINE

Senator MURRAY. Thank you. Dr. Fauci, you talked a little about this. But I wanted to go back through it again. I am really pushing for Congress to pass additional emergency COVID funding to make sure that our communities have the tests, and the treatments, and vaccines they need to keep their families safe.

And I understand your Institute is supporting research on the development of these next-generation vaccines that could protect against multiple variants. What can you tell us about the progress of that research? And what does NIH need to see it to completion?

Dr. FAUCI. Well, thank you for that question. Well, the progress has been substantial. To get what we call "universal", and that is probably too broad a term, is to get a vaccine that works against multiple variants of SARS-CoV-2 is the first step.

And that would be something where you get a vaccine that either is directed against the common component of all of the variants, or has each of the components of the variants, for example, in a nanoparticle with a mosaic or multiple components to it.

We have studies that are, right now, gone from preclinical, namely, in an animal model, into a human study, and the results actually look very promising. The next step would be to get a vaccine that not only is against all variants of SARS-CoV-2, but against all of those group of variants, including, what we call, sarbecoviruses, which overlap with the viruses that we see in many bats, which almost certainly are the original source of these viruses, that have jumped species and gone into humans.

The work is going along very, very well. We are getting a number of investigators, both people who have been established in the field, and new investigators, but we can't continue it, Madam Chair, without additional resources.

And that is really one of the things that is very, very difficult for us, because the scientific opportunity is there, and we really feel

that we do have this, not only as an aspirational goal, but we will be able to get to that goal of getting a vaccine that would protect us against both known and unknown variants. So we are excited about the science of it, but we can't continue without additional resources.

INTERAGENCY WORK WITH BARDA

Senator MURRAY. To have resources, right. And how is your Institute working with BARDA (Biomedical Advanced Research and Development Authority) to accelerate innovation in the next-generation vaccine development, particularly for COVID-19 vaccines?

Dr. FAUCI. Well, we have had a long-standing collaboration and cooperation with BARDA now for quite a long period of time. And the way that works is that we do the fundamental, basic research, and proof of concept, and very often get involved, not only in the preclinical, but in the early trials, whereas, BARDA partners with a pharmaceutical company to do the advanced development of these concepts.

So it is a partnership that has really worked very, very well, and hopefully we will be able to continue that, again with the need for new resources.

Senator MURRAY. Okay. Thank you.

Dr. Gordon, I want to come back to you. You have had several questions about mental illness, not surprising. It is a huge issue for America today. And I know that despite the best efforts of researchers, like yourself, in the past 30 years, we have seen dramatic increases in mortality, morbidity, and healthcare costs related to mental illness; and that is actually before factoring in the effects of this pandemic, and the opioid crisis.

MENTAL HEALTH DIAGNOSIS ISSUES

And on top of it all, diagnosis is really difficult. And medications don't always work, and can have awful side effects. So I know Senator Blunt asked you about using RADx, as one possible approach, but what are the greatest barriers to accurate diagnosis?

Dr. GORDON. Well, frankly, one of the greatest barriers to accurate diagnosis, Senator, is that our diagnoses are not terribly good, in terms of describing what is going on in the brain. And so we need a better individualized approach, not just to diagnosis, but really being able to make informed clinical decisions in cooperation with our patients.

Well, the clinical issue really isn't, does this individual have depression, or schizophrenia, or bipolar disorder, although those diagnoses can be sometimes hard to differentiate in the individual patients.

The bigger clinical question is: For this patient with depression, are they going to benefit most from a medication, or which type of medication? Or are they going to benefit most from psychotherapy, or a brain stimulation treatment?

We have a number of different research projects that are aimed at trying to make those kinds of clinical decisions with the aid of technology, with the aid of increased attention to details in the patients' behaviors, and cognitions. And that approach I think is

going to take advantage of things like big data. So we need to collect lots and lots of information about—well characterized patients.

And then we need to make careful experiments to try to determine when that information helps us describe that patient better. So it is really about precision medicine in psychiatry, moving it forward in a number of different fronts, from grants, to academic organizations. And as I mentioned also before, small business grants that are really paying off. So we should see some progress, hopefully in the future, near future.

Senator MURRAY. So I assume it is fair to assume that solving this diagnosis puzzle, will really open doors for better treatments?

Dr. GORDON. It would open doors to transforming how we decide with our patients what treatments to use. It would really change psychiatry. Right now, as a psychiatrist, if I want to help someone with depression, our only discussion is about which side effects they don't want. And so we try to avoid one medication or another. As opposed to which medication, or which treatment that I have to offer is going to work better for them. So yeah, it would really transform things.

Senator MURRAY. Okay. Thank you. Senator Blunt.

Senator BLUNT. Thank you, Chair.

ADUHELM

Dr. Hodes, I have been watching the FDA decision on Aduhelm, the Biogen drug, as well as the CMS (Centers for Medicare & Medicaid Services) handling of that. I think that decision is going to have some pretty long-term consequences, particularly the CMS decision, and other companies will be following. Biogen has already made some pretty dramatic decisions, based on the CMS view that only the people in a trial could benefit from the emergency approval, by FDA.

Would you talk a little bit about both of those things? First the FDA approval process, what merit do you see in that emergency approval process? And then, what concerns do you have or not have about CMS then deciding that it would only be available to a few people?

Dr. HODES. Thank you for the question. Well, of course FDA and CMS have their regulatory responsibilities, and we defer to those. But we do work very closely particularly on the science involved in these implications; so as many, or all of you may know, the decision by FDA was what was called an accelerated approval of Aducanumab, Aduhelm, based on its ability to clear amyloid from the brain, and by brain scans.

Without compelling evidence of clinical effectiveness, and that was the rub. And in fact, the FDA decision required that the sponsors, Biogen, Eisai, then conduct a randomized, controlled trial to look if—to determine if there was, in fact, clinical outcome.

It was in that setting that CMS said that for widespread coverage it would require randomized, controlled clinical trial. It made the distinction, though, about the future of such drugs. Any drug that received an approval based on clinical outcome, based on FDA decision and judgment, would have broader coverage without requirement for another randomized clinical trial.

But any in which there was no demonstrated evidence of effectiveness on clinical outcomes, would require that kind of outcome before they went further. Again, those are regulatory decisions.

Senator BLUNT. So it sounds like, to me, the FDA decision was really a CMS; or at least just the decision to continue the trial. That may not have been what FDA thought it was doing, but that is what CMS decided it was doing?

Dr. HODES. No. FDA, again, by requiring that—for maintenance even of the accelerated approval, that a clinical trial, a randomized trial, be carried out, was also saying there needed to be a continuation.

You asked, importantly I think, what the impact of this will be on other studies, other agents. There are currently three companies, Roche, Lilly, and Eisai—Biogen, which have ongoing clinical trials of other antibodies to amyloid, they have all received a breakthrough designation last year from the FDA. They are all expected to produce their results in the next few months. So above all, I think we all share hope and optimism that will see effective clinical outcomes there.

For NIH, I think the implications are clear. We need to support the most rigorous and continuing research toward amyloid and other targets, the kind of research that will give clear-cut, definitive answers about clinically important outcomes. And that is certainly our part in this consortium.

VACCINE AND THERAPEUTIC DEVELOPMENT

Senator BLUNT. Well, Dr. Fauci, while we are talking about the accelerated approvals, or not, during COVID, obviously NIAID (National Institute of Allergy and Infectious Diseases) shepherded both successful vaccines and therapeutics, through the approval process during the pandemic. I am concerned that once the pandemic is officially behind us that both vaccine and therapeutic research and development will be subjected to normal development processes that, in what we have learned in the last year-and-a-half may not be the structure that we should use. Would you talk about that a little bit?

Dr. FAUCI. Senator, are you referring to the fact that we should not slow down the acceleration of approvals when we are out of the pandemic phase?

Senator BLUNT. I am asking that, or if there should be some “new normal” approval process, now that we have had, I think two vaccines, and 20 treatments developed through those partnerships?

Dr. FAUCI. Yes. I am not sure I understand the question. It is my fault. Are you saying that, should we continue the normal standard of approval, which would take much longer than the emergency-use authorization? Is that the question you are asking?

Senator BLUNT. That is the question.

Dr. FAUCI. Yes. Yes, I think we should go through the normal approvals, and if we are in an emergency situation again, we absolutely should use the EUA (Emergency Use Authorization) approach which has fared us very well. But when we get behind us the outbreak, I think the normal approval process, which is pretty much expedited pretty well by the FDA, should continue.

Senator BLUNT. All right. Thank you, Chairman.

Senator MURRAY. Senator Kennedy.

TITLE 42 RECISSION

Senator KENNEDY. Thank you, Madam Chair. Did the Biden administration ask any of you whether it was safe to rescind Title 42?

Dr. TABAK. We have had no discussions about that, sir.

Senator KENNEDY. You haven't done?

Dr. TABAK. I have not. No.

Senator KENNEDY. How about you, Dr. Fauci?

Dr. FAUCI. No. I have not.

Senator KENNEDY. How about you, Dr. Gibbons?

Dr. GIBBONS. No, No, sir.

Senator KENNEDY. How about you, Dr. Gordon?

Dr. GORDON. No.

Senator KENNEDY. Dr. Hodes?

Dr. HODES. No, sir.

Senator KENNEDY. Dr. Volkow?

Dr. VOLKOW. No.

Senator KENNEDY. Well, the Biden administration says it is safe, that under the science it is okay. Who did the administration rely on, to suggest that rescinding Title 42 is in the interest of public safety?

Dr. FAUCI. That was a CDC decision. The Title 42 is a CDC decision.

Senator KENNEDY. Do you agree with it, Dr. Fauci?

Dr. FAUCI. Well, I think that the immigration policy should be separated from the public health—

Senator KENNEDY. No. And I don't want to get you involved in immigration policy; but people are people, physiology is physiology.

Dr. FAUCI. Right.

Senator KENNEDY. And one is the susceptibility of the virus has nothing to do with their country of origin or immigration status.

Dr. FAUCI. Right.

Senator KENNEDY. And what I am asking you, purely from a public safety standpoint.

Dr. FAUCI. Right. Yes.

Senator KENNEDY. Is it safe to rescind Title 42?

Dr. FAUCI. I think given the level of infection at the time, which is right now, that I think that the CDC decision was a reasonable decision.

Senator KENNEDY. Does anybody disagree with that? Do you all agree with that? Let me get you, of record.

Dr. Gibbons?

Dr. GIBBONS. Yes. I concur with Dr. Fauci on that.

Senator KENNEDY. Dr. Gordon?

Dr. GORDON. I don't have the expertise to concur or not concur.

Senator KENNEDY. Okay. Dr. Hodes?

Dr. HODES. I would also say I don't have the expertise to weigh on this.

Senator KENNEDY. Dr. Volkow?

Dr. VOLKOW. I don't have the expertise.

Senator KENNEDY. Okay. All right; thank you very much.

Senator MURRAY. Senator Moran.

ARPA-H PRIORITIES

Senator MORAN. Thank you, Chairman Murray. I don't have the benefit of knowing what has been asked and answered. So I will ask questions. Recently the ARPA-H proposal would initially focus—this is for Dr. Tabak—would initially focus on three diseases: cancer, Alzheimer's, and diabetes, and be housed under NIH.

Congress and NIH already invest significantly into research and development to these three diseases. How can NIH conduct proper oversight to ensure NIH, through its current work, isn't simply being replicated?

Dr. TABAK. I think those three diseases are meant to be illustrative and not restrictive. In terms of the larger issues that you raise, as you know, NIH does a rather extensive portfolio analyses, and the expectation would be that there will be a crosstalk between the new agency, and the NIH to avoid, as you put, you know, the potential for duplication.

ALZHEIMER'S DISEASE TREATMENTS

Senator MORAN. This is again for you, Dr. Tabak. In recent National Coverage Determination, CMS indicated it would support FDA and NIH, by covering drugs for Medicare beneficiaries, participating in randomized, controlled trials. I would interpret that to mean that there is a path to coverage through NIH studies for participants qualifying trials, related in the FDA-approved Alzheimer's disease treatments. Is that an assessment that—and I am not—if that is an accurate assessment? Or how would you elaborate?

Dr. TABAK. If I may turn to Dr. Hodes, who is the expert in that space.

Senator MORAN. Dr. Hodes.

Dr. HODES. I think that is a very accurate statement. Thank you.

Senator MORAN. Good. And that is a good development, right? Dr. Hodes shook his head, yes.

Dr. HODES. Yes, sir.

NCI BUDGET REDUCTION

Senator MORAN. Let me talk a moment, in the absence of Dr. Sharpless, I will let you all direct who should answer my question. The NIH 2023 budget request suggests \$199 million cut to the NCI (National Cancer Institute), a 2.9 percent cut from the current fiscal year. I assume that that will be explained as those dollars being picked up in ARPA-H. What is the rationale for the significant funding pivot to ARPA-H at the expense of NCI?

Dr. TABAK. So at the time the budget was prepared, the only baseline that the administration had to work with was a continuing resolution level. We are fortunate that the Congress, in the Omnibus, provided us with substantially more resources than were in the continuing resolution. And we certainly look forward to working with you as the 2023 appropriations process works through.

Senator MORAN. So there is room—there is no particular insistence that that is the right ratio between the funding of one ARPA-H, and the normal appropriations process for NCI?

Dr. TABAK. I think it is more than a reflection of using a baseline that was available at the time.

Senator MORAN. Well, the \$16.9 billion increase for NCI in fiscal year 2022, allowed the NCI to increase the funding allocated toward competitive cancer grants. It is one of the reasons we continue to advocate for higher NCI funding, is to improve NCI's ability to award those competitive cancer grants.

In recent years NCI could only fund about one in eight research grant applications. Dr. Sharpless indicated, in front of the subcommittee, that that was a great concern to him, as it is to me. If NCI funding is not boosted above the fiscal year 2022 levels, can competitive grants be prioritized and expanded?

Dr. TABAK. It would be very difficult to do that in the absence of additional funding.

Senator MORAN. Doctor, thank you, both of you. Thank you all.

AUTOIMMUNE DISEASE RESEARCH

Senator MURRAY. Dr. Tabak, last week the National Academy has issued its review of NIH's autoimmune research portfolio, and the authors found that much of the work that that agency does in this area is really extraordinary. But that NIH doesn't do the best job coordinating, or setting priorities, or focusing on innovation, or evaluating its autoimmune research portfolio.

The authors' findings really echo an earlier 2010 National Academy Study on women's health research, and to address these problems, they recommended the creation of an Office of Autoimmune Disease Research within the Office of the Director, to facilitate collaboration and coordination.

Given the importance of this research for communities across the country, it is critical that NIH does the best possible job facilitating it. Do you have concerns with establishing this office?

Dr. TABAK. Senator, the report, as you know, was released last week, and we are still reviewing the specifics of it. In reviewing the top line messages, among the things they suggest that we do, develop an agency-wide strategic plan, make sure that investments that we make align with those strategic plans, coordinate both within and outside the agency, do evaluation, do reports to the Congress.

At first glance, I think these are things that we could probably do without the creation of a new office, but I certainly, you know, would be willing to work with you, and other members of the committee, going forward, as we sort through the specifics of the report, and get a better understanding of the rationale behind their specific recommendation.

Senator MURRAY. Okay. I would like to work more with you on that. I think this is extremely important. I want to make sure we are addressing it in the correct way, and I want to talk to you more about that.

Dr. TABAK. Thank you.

Senator MURRAY. Senator Blunt.

EARLY STAGE INVESTIGATORS

Senator BLUNT. Thanks Chair. I think my last question today will start with Dr. Tabak, but anybody that wants to talk about it.

One of the things we were most concerned about 8 years ago was the fact that young researchers were leaving the field. That the pool of money, not only wasn't increasing, but it was about 22 percent less in the research buying power, than it had been.

What are we doing right now to keep young researchers in the field, and try to see that they get their first grant, and that there is not an obstacle based on numbers of first grants to getting that second grant?

Why don't you start, Dr. Tabak? And if anybody else wants to talk about what you are doing to keep young researchers engaged I would be pleased to hear that.

Dr. TABAK. We have prioritized the funding of early-stage investigators; back in 2013 we only supported 600 such individuals, last fiscal year, 1,513. That has come as a result of the Institute and Center leadership prioritizing applications from these individuals. We have also created certain mechanisms that would incentivize and enable early-stage investigators.

So for example, we have the so-called Katz Early Stage Investigator Award, in which no preliminary data is accepted. This is important, it basically liberates a new investigator from his or her post-doctoral or graduate school experience, and they are able to think, you know, as boldly as possible in preparing an application.

We also have the NIH Director's New Innovator Award Program which is attracting early-stage investigators from very broad biomedical fields. And so when you take these things together, I think we are making good progress in ensuring the entrée into the system of biomedical research.

But let me turn to my colleagues to see if anybody else wishes to comment.

Dr. GIBBONS. If I might add to Dr. Tabak's comments. There are two areas for the NHLBI (National Heart, Lung, and Blood Institute) that we are particularly focusing on. As evident in these hearings, a critical element is the translation of basic science understanding into clinical science and clinical medicine, and clinician scientists are critical to making those transitional leaps that are so important to public health.

And this is an area, quite frankly, where there is a paucity of early-stage investigators, in a critical pipeline. And so we have special awards for them to get their first RO1, in particular, to launch their careers as early-stage clinical investigators.

I would also add the diversity of that early-stage investigator pool is critical, and recognizing the supportive efforts to expand that diversity is, again, another high priority which we have programs, specifically, designed to do that, like our PRIDE Program. Over.

Senator BLUNT. Anybody else?

Dr. HODES. I had to reinforce the points made. And note that we also try to track outcomes of our programs, including training, career development. So for example, with the expanded research around Alzheimer's and related dementia's research, since 2015 through the present, fully a third of the investigators awarded have been new and early-stage investigators who have had no prior, major NIH research. And we think this is an important reflection

of our ability to recruit. And now we will see about retaining them into the research workforce.

Dr. VOLKOW. And I was just going to make a comment, because Dr. Tabak alluded to it, and an area that is crucial is to ensure that we get the brightest interested in science; so going after younger kids, and teaching them, and giving the opportunity to see what science is all about, is a way that you can ensure that you will have the throughput then, to get investigators.

Senator BLUNT. Thank you, Chair.

Senator MURRAY. Thank you. Senator Moran.

Senator MORAN. I will just take this moment, Chairman Murray, to thank you and Senator Blunt, for your leadership, and the success that we have had in numerous years, now in a row, in the support for the National Institutes of Health.

I have been a ranking member of this committee with Senator Harkin. You both have been ranking members, and chairmen and woman of this committee during a period of time in which we were capable, in a bipartisan way, of increasing the investment in fighting the diseases and afflictions that Americans and people around the globe suffer from.

And not knowing what our committee schedule is into the future, this may be the last time we have Senator Blunt here with the NIH crew. And I take this moment to thank him, in particular, for his efforts that have been recognized around the country, and certainly in our home States of Kansas and Missouri, of making a tremendous difference in the efforts to find the cures and the treatments to reduce the afflictions that we face in the world, of our well-being, of our health.

And so to you, to Senator Blunt, particularly today, thank you for that leadership. I am pleased that the world is in a better position, and that Americans have a greater chance of fighting these diseases, and there is a lot more hope than there used to be.

Senator MURRAY. Thank you. Thank you for those comments. I think we all agree.

That will end our hearing today. And I want to thank my fellow committee members for a thoughtful conversation.

I want to thank Doctors Tabak, Fauci, Gibbons, Gordon, Hodes, and Volkow. Thank you all for joining us today to share your expertise.

ADDITIONAL COMMITTEE QUESTIONS

For any Senators who wish to ask additional questions, questions for the record will be due May 27, at 5:00 p.m.; the hearing record will 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. LAWRENCE TABAK

QUESTIONS SUBMITTED BY SENATOR PATTY MURRAY

Question. The budget request concentrates most of its proposed spending increase in ARPA-H, even though that agency has yet to hire anyone. If Congress funded ARPA-H at \$5 billion as the budget proposes, what impact would that have on N-

I–H’s 27 institutes and centers? While Congress’s work on the ARPA–H authorization continues, there’s broad agreement that it should not be based in Bethesda with the rest of NIH and that its staff should be recruited from outside the agency. Given the transformative role ARPA–H is supposed to play by supporting high-risk, high-reward research, I believe NIH should rely on outside expertise to recruit the right staff to stand up the agency.

Who is handling ARPA–H’s hiring? Is it NIH or an outside firm?

When does NIH expect to have a permanent director on-board?

Answer. HHS is in the process of standing up ARPA–H and developing plans for its operations and functions, including recruiting an innovative group of people to help launch the important work of the agency. HHS is bringing onboard staff in key support functions—acquisitions, budget/finance, and strategic resources. Program managers will be recruited after an inaugural director is on board. The Secretary is also seeking to identify an interim leader prior to the appointment of an inaugural Director. Ideally, this acting deputy director would have considerable experience in government—specifically familiarity with the “ARPA” model, broad technical and management experience across several disciplines, and a proven record innovating around experimental platforms and tools to facilitate discovery, quantification, and validation of fundamental measures in science.

Meanwhile, the White House is currently looking for candidates for President Biden to appoint as an ARPA–H Director who will be responsible for administration and operation of ARPA–H and who will report to Secretary Becerra. The ideal candidate would be an extraordinary leader with a vision and proven track record for driving transformative change in health and biomedicine, a strong private sector background, and experience in academia or government, as well as a proven ability to build partnerships.

Question. Congress provided significant funding for research into long-COVID with the goal of understanding this complex condition and developing potential treatments.

When does NIH expect to exhaust its existing balances of long-COVID funding and what steps would it take if faced with a shortfall?

Answer. Funds for the Researching COVID to Enhance Recovery (RECOVER) initiative are being used to implement the necessary in-depth and national scale approach to understanding, preventing, and treating the post-acute sequelae of SARS–CoV–2 infection (PASC), including Long COVID. The National Institutes of Health (NIH) has either obligated or has planned/outyear RECOVER activities for all of the \$1.15 billion funding provided by Congress. Working on an accelerated schedule, NIH has obligated approximately \$674.5 million as of May 17, 2022. The balance will be utilized in planned obligations to cover fiscal year 2022 and outyear spending for RECOVER studies.

Our understanding of the complexity and broad range of conditions encompassed in PASC has evolved substantially since the time of the original appropriation, and it is clear that we need to further accelerate and expand our existing efforts and capacity to test a wider range of interventions and develop assays for the diagnosis and monitoring of patients with PASC.

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

ARPA–H

Question. I am a supporter of ARPA–H. At last year’s NIH hearing I spent the majority of my statement highlighting that ARPA–H is the right idea at the right time because, as we learned so well during COVID–19, NIH can take a larger, more involved role in public-private partnerships without overstepping the bounds of the role private industry should play. Since that time, Congress has passed an Omnibus appropriations bill that included \$1 billion to establish ARPA–H. In addition, the HHS Secretary has established ARPA–H at NIH, but with direct reporting to the Secretary’s office. Dr. Tabak, can you explain why it is important to have ARPA–H under the NIH umbrella, and specifically how this will help get ARPA–H established and working on research programs faster?

Answer. On April 15, 2022, Secretary Becerra transferred ARPA–H to the NIH as notified in the Federal Register published April 20, 2022. The Secretary indicated that, following presidential appointment, the ARPA–H director will report directly to the Secretary and be delegated all the necessary authorities to administer ARPA–H.

The Secretary’s decision to transfer ARPA–H to NIH is critical to accelerating ARPA–H’s establishment and reducing the use of funding for redundant functions using critical infrastructure provided by NIH. Broadly, ARPA–H’s mission aligns

with NIH's, in that both agencies strive to improve health through research. Through close collaboration between ARPA-H and NIH, along with other Federal, and public or private entities, ARPA-H will ensure it reaches all people with better health solutions faster. ARPA-H benefits from drawing closely upon NIH's role as a global leader in biomedical research, including its knowledge, expertise, and ongoing activities. Setting up ARPA-H within NIH will avoid unnecessary duplication of scientific and administrative effort. As a part of NIH, ARPA-H is benefitting from and leveraging the use of several electronic systems to quickly establish its functional areas, provide for a more seamless start up, and avoid building functionality from scratch that already exists.

Question. ARPA-H is in the process of being stood up. Can you provide the Committee with additional details on:

What qualifications you are looking for in a Director?

Answer. President Biden will appoint an inaugural Director with the requisite experience to lead this new agency. An ideal candidate would be an extraordinary leader with a proven track record and vision for driving transformative change in health and biomedicine, a strong private sector background, and experience in academia or government. In addition, the candidate should have a proven ability to build partnerships.

Question. When do you expect a Director to be in place?

Answer. The White House manages the search, nomination, and announcement, of all presidential appointees.

Question. How many program managers are you looking to hire?

Answer. ARPA-H will recruit and hire program managers based on the organization's priorities and the funding available. Decisions will be made when the inaugural ARPA-H Director is appointed.

Question. What are the qualifications for the location for an ARPA-H headquarters and when will that decision be announced?

Answer. HHS is in the process of standing up the new agency and is developing plans for its operations and functions. Currently, no commitments as to the physical location of ARPA-H have been made.

Question. Will there be an official location search similar to how locations for other agencies outside of Washington, DC were chosen? Like the recently relocated National Institute of Food and Agriculture?

Answer. Currently, no commitments as to the physical location of ARPA-H have been made. We will continue to engage in a thoughtful process.

Question. When do you expect scientific programs to begin?

Answer. Scientific programs are expected to begin after the appointment of an inaugural director and the recruitment and hiring of the first program managers.

Question. How will ARPA-H be structured to ensure that biomedical researchers at universities have an opportunity to be program managers when typical sabbaticals from research institutions last 2 years, which is less than the typical three year program manager term?

Answer. Program managers are expected to be appointed for a single three-year term with the possibility of a single renewal, but shorter terms could be negotiated. In a circumstance where a program manager's home institution recalled the researcher prior to the end of an appointment, ARPA-H would anticipate working with the institution for a mutually agreeable solution.

Question. Will ARPA-H encourage researchers to publish outcomes of their ARPA-H research in medical publications? This is currently atypical at DARPA.

Answer. DARPA and ARPA-H operate in two different ecosystems. DARPA funds performers to benefit the Department of Defense in execution of its mission. ARPA-H's goal is for new technologies, capabilities, and platforms to benefit everyone and improve everyone's health potential. Where appropriate, ARPA-H performers will be encouraged to publish their findings or otherwise make them widely available.

Question. Will ARPA-H run clinical trials? If so, what will be the process to test/approve treatments or vaccines with FDA?

Answer. Scientific programs are expected to begin after the appointment of an inaugural director and the recruitment and hiring of the first program managers. A potential area of focus is to improve clinical trials to speed the generation of research results and recruit more inclusive trial participants so that those results are more representative of the patient population. ARPA-H will seek opportunities to work closely with other Federal agencies and the private sector on these issues.

Question. More specifically, how do you envision the partnership between ARPA-H and FDA?

Answer. See Answer above.

Question. How do you ensure the FDA approval process does not hinder the urgency ARPA-H will need?

Answer. Operating within the Federal Government, ARPA-H anticipates the benefit of forming close relationships, collaborations, and agreements with other Federal agencies, either formal or informal. In either case, the intent remains the same—to work closely with other Federal agencies to engage them early in the program development process and collaborate to promote synergistic goals.

Question. Are you concerned that FDA will hinder the fast moving nature of the agency because of their slow approval process?

Answer. ARPA-H anticipates partnering with the FDA through collaborative integration and involvement of FDA staff, where appropriate, in relevant programs from their inception. These collaborations would be developed to be mutually beneficial from ARPA-H's and FDA's perspective.

Question. Will ARPA-H have an advisory board? If so, who will comprise it? If not, why not?

Answer. This would be decided by the inaugural Director.

Universal Flu Vaccine

Question. In response to the COVID-19 pandemic, the US was able to work through public-private partnerships to develop several vaccines within less than a year. While this was a much needed triumph, I assume, Dr. Fauci, it also greatly increases expectations that we can develop vaccines for other diseases using the mRNA model or the processes used for developing a COVID vaccine. What did you learn from COVID-19 vaccine research and development that can now be applied to the development of other vaccines, particularly a universal flu vaccine?

Answer. The development of vaccines for COVID-19 was greatly accelerated by the development of vaccine platform technologies as well as advances in structural biology that allowed for the stabilization of the SARS-CoV-2 spike protein and its incorporation into the mRNA vaccine platform. Research advances that have supported the development of COVID-19 vaccines, including current efforts to develop the next generation of COVID-19 vaccines, will support ongoing efforts to develop universal influenza vaccines by further validating and advancing the vaccine platforms and technologies on which they are based. For example, advances in mRNA vaccine platforms, including the successful development of mRNA-based COVID-19 vaccines, have shown the utility of this vaccine platform, especially in situations where rapid development of vaccines is crucial or where traditional vaccine technologies have not yet proven successful. Several mRNA-based vaccine candidates for seasonal influenza are currently undergoing clinical testing. The National Institute of Allergy and Infectious Diseases (NIAID) also is sponsoring clinical studies of three novel mRNA-based HIV vaccines. Evaluation and development of the mRNA vaccine platform across a number of diverse virus families will further aid our efforts to develop tools and resources for responding to the next pandemic threat.

NIAID also will build on the advances made for COVID-19 vaccines using other vaccine platforms, many of which are already in use for the development of universal influenza vaccines. NIAID Vaccine Research Center investigators have created a nanoparticle-based pan-coronavirus vaccine candidate designed to elicit antibodies targeted to the spike protein of multiple different coronaviruses. This mosaic nanoparticle-based approach—based on the universal influenza vaccine concept known as FluMos—is currently undergoing preclinical testing in an animal model. Separately, NIAID-supported scientists provided proof of principle that self-assembling mosaic nanoparticles displaying receptor binding domains of multiple coronaviruses in the Sarbecovirus subgroup (including SARS-CoV-2) can induce protection in mice when challenged with another Sarbecovirus. These advances in nanoparticle vaccine technology will help inform similar strategies for development of a universal influenza vaccine. In addition, NIAID intramural investigators are evaluating inactivated whole virus vaccine candidates for a broadly protective beta-coronavirus vaccine based on related efforts to develop a universal influenza vaccine. Development and testing of this approach for beta-coronaviruses will provide valuable insights into the development of broadly protective inactivated whole virus vaccines for influenza and other viral families. NIAID also is supporting studies through its vaccine adjuvant program to compare different classes of adjuvants and identify the most efficacious vaccine formulations. The identification of vaccine adjuvants that promote cross-protective and durable immunity in vulnerable populations would complement ongoing efforts to develop universal influenza vaccines as well as vaccines for other pandemic threats.

In late 2021, NIAID announced four awards to fund multidisciplinary, collaborative teams to conduct research on pan-coronavirus vaccine candidates and help accelerate pan-coronavirus vaccine development. The teams will incorporate advances in coronavirus biology and immunology; immunogen design; and innovative vaccine and adjuvant technologies to discover, design, and develop vaccine candidates to

protect against multiple SARS-CoV-2 variants and other coronaviruses. NIAID expects that these efforts not only will advance the development of pan-coronavirus vaccines, but also will complement similar activities undertaken by NIAID intra- and extramural researchers, including at the Collaborative Influenza Vaccine Innovation Centers (CIVICs) and the NIAID-supported Vaccine and Treatment Evaluation Units (VTEUs) to develop universal influenza vaccines. In addition, NIAID-supported research to better understand the immune response to SARS-CoV-2 infection and vaccination, including the role of antibodies and T cells, will further advance our understanding of the human immune system and may provide valuable insights into new strategies for developing and evaluating broadly protective vaccines for other pandemic threats, including influenza.

Long COVID

Question. Dr. Tabak, there are a lot of unknowns about long COVID—what the causes are, why it affects only some, even what the defined set of symptoms are—and that opens up a lot of research avenues. But there is also a sense of urgency that should not be lost and NIH must stay focused on finding ways to help those who suffer, which could be as many as 30 percent of the population that has had COVID-19.

At the end of 2020, Congress provided \$1.15 billion for research on long COVID. Using this funding, NIH started the RECOVER program, which in the intervening months has received a lot of criticism. Concerns have been raised about NIH's lack of urgency and whether it is focused too much on open-ended research questions as opposed to testing treatments and moving therapeutics to clinical trials. Can you address these concerns and specifically highlight why NIH chose to create a large observational study as opposed to focusing on testing therapeutics and other possible treatments?

Answer. Researching COVID to Enhance Recovery (RECOVER) program's national longitudinal observation study is enrolling thousands of diverse participants including adult, pregnant, and pediatric populations from over 200 sites across the country, to fully understand the incidence, prevalence, clinical signs, and symptoms of the various forms of post-acute sequelae of SARS-CoV-2 infection (PASC) and risk factors for their development. Of note, RECOVER is particularly attentive to ensuring inclusion of those typically underrepresented in biomedical research and those from the populations disproportionately affected by COVID-19. The clinical data and specimens from this study are necessary to provide the robust evidence base for development of diagnostics, clinical monitoring strategies, as well as therapeutics. Moreover, the data collected through this study will inform an understanding of and strategies to address ethnic and racial disparities in PASC, impact on pre-existing conditions, and mental health effects.

Key data and findings from RECOVER's observational study have ensured that NIH is now better poised to test currently available treatments and agents to address symptomatology while simultaneously continuing efforts to fully understanding the full spectrum of diagnosis for the pathobiology of PASC—efforts that have not occurred in research of other post-viral conditions. For example, with knowledge gained through the observational study and other elements of RECOVER, potential clinical trial interventions could explore pathways to determine if there are viral responses that might generate some sort of reaction (e.g., pro-inflammatory) that can be treated or to determine if there are other types of disorders producing metabolic aspects that can be therapeutic targets.

Clinical trials to identify safe and effective treatments as well as preventive strategies for PASC are a priority for NIH. NIH is addressing symptoms/symptom clusters and underlying mechanisms of pathobiology of PASC by establishing a dedicated Clinical Trials Data Coordinating Center to implement and manage multiple interventions, as well as issuing a solicitation for well-designed clinical trials testing a range of interventions. Clinical trial development is being informed through a consultative process with engagement of patient, practitioner, and research communities regarding symptoms/symptom clusters, outcome measures, and interventions. The first trials are anticipated to be launched by Fall of 2022.

The RECOVER initiative is also leveraging real-world data derived from the electronic health records (EHRs) of over 60 million adult and pediatric patients accessible through the National COVID Cohort Collaborative (N3C), the PEDSnet consortium, and the National Patient-Centered Clinical Research Network (PCORnet).^{1,2,3}

¹ <https://ncats.nih.gov/n3c>.

² <https://pedsnet.org/>.

³ <https://pcornet.org/network/>.

RECOVER electronic health records (EHR) to better define PASC in all its forms, to discover and understand factors that influence the likelihood of developing PASC in adults and children, to understand PASC treatment strategies as quickly as possible, and to identify high priority approaches to address PASC in the populations most affected. While this work is ongoing, the RECOVER EHR studies have recently completed their initial set of analyses at national scale and are publishing results on several key clinical and public health issues including: PASC cardiac complications;⁴ development of new onset diabetes as part of PASC; impact of COVID-19 vaccination and viral variants on PASC; manifestations of PASC in children and adolescents; and racial, ethnic, and socioeconomic disparities in PASC.

The RECOVER pathobiology studies being launched soon will identify mechanisms underpinning clinical phenotypes and symptomatic manifestations and understand the pathology in multiple organ/systems that has led or will lead to clinically significant health problems. Analyses of clinical data and biospecimens from the longitudinal studies will contribute to our understanding of the cause(s) of PASC, help identify biomarkers, enable risk stratification, contribute to the development of new therapeutic targets, and will help inform the design of PASC clinical trials.

A systematic and standardized autopsy study at scale is underway now to comprehensively identify the effects of SARS-CoV-2 infection on organs/tissues throughout the body for the purpose of understanding the pathobiology of PASC and informing development of diagnostics, clinical monitoring, and potential treatment and prevention strategies.

Osteopathic Medicine

Question. Dr. Tabak, Colleges of Osteopathic Medicine educate nearly a quarter of U.S. physicians, but only compromise a small portion of NIH grants and are underrepresented on NIH study sections and advisory boards. How will NIH work with Colleges of Osteopathic Medicine to increase their representation on NIH panels and through funding opportunities?

Answer. The National Institutes of Health (NIH) is dedicated to strengthening and diversifying the biomedical research workforce. This includes fostering opportunities for physician-scientists with osteopathic medical degrees, a group of researchers NIH recognizes as being underrepresented in the biomedical workforce. As part of this effort, NIH continues to address recommendations described in a 2014 report focused on the physician-scientist workforce from the NIH Advisory Committee to the Director.⁵ As the report notes and NIH agrees with, “findings which lead to advances in practice are driven largely by the work of investigators with a variety of degrees [including D.O.s], of whom those with clinical training contribute essential knowledge and skills.”

Physicians with a Doctor of Osteopathic Medicine (D.O.) degree represent an important component of the medical community. They straddle the complementary, integrative health, and allopathic medical communities and have historically been connected to the National Center for Complementary and Integrative Health (NCCIH), one of NIH’s Institutes and Centers (ICs), through the practice of osteopathic manipulation. Osteopathic manipulation is a full-body system of hands-on techniques to alleviate pain, restore function, and promote health and wellbeing. This promising intervention is of interest to NCCIH, and the Center makes every effort to ensure that D.O.s have representation on its advisory council. NCCIH currently has two members with a D.O. degree on its 18-member council.⁶

NCCIH along with other NIH ICs has specific opportunities for clinician-scientists, which includes D.O.s, who conduct research across a wide range of complementary and integrative health approaches. Examples of such programs include, but are not limited to:

- Mentored Clinical Scientist Research Career Development Awards.⁷
- K12 career development award program.⁸
- Academic Research Enhancement Award (AREA) program.⁹

Act for ALS

Question. Last year, Congress passed a bill I cosponsored, ACT for ALS, that establishes a grant program to address neurodegenerative diseases, and specifically ALS. The fiscal year 2022 Omnibus passed in March provided \$25 million to establish the program. Dr. Tabak, I know NIH had concerns about this bill when it was

⁴ <https://www.cdc.gov/mmwr/volumes/71/wr/mm7114e1.htm>.

⁵ acd.od.nih.gov/documents/reports/PSW_Report_ACD_06042014.pdf.

⁶ www.nccih.nih.gov/about/nacch-member-roster.

⁷ researchtraining.nih.gov/programs/career-development/K08.

⁸ researchtraining.nih.gov/programs/career-development/k12.

⁹ grants.nih.gov/grants/funding/r15.htm.

passed. Can you discuss the concerns and the challenges to this research so we can address them moving forward?

Answer. The National Institutes of Health (NIH) strongly supports investing in the unique and specific research needs of the Amyotrophic lateral sclerosis (ALS) community. ALS and other rare and fatal neurodegenerative diseases inflict immense suffering on people living with these diseases and their families, and there is an urgent need to develop effective therapies and cures. NIH is enthusiastic about partnering with others to catalyze new approaches capable of bringing us closer to developing effective interventions to prevent, diagnose, mitigate, treat, or cure ALS.

NIH is supportive of the ACT for ALS provisions that have the main intent of broadly enhancing research and development for ALS and other rare neurodegenerative diseases, including the HHS Public-Private Partnership for Rare Neurodegenerative Diseases, and the U.S. Food and Drug Administration (FDA) action plan and grant program for research on ALS and other rare neurodegenerative diseases. NIH has major capabilities in administering grant programs in ALS research. NIH's primary concerns with the legislation have been with the grant program for research utilizing data from expanded access to investigational therapies for ALS authorized in section 2 of the legislation. NIH's concerns continue to be that (1) the creation of the expanded access grant program fails to place appropriate focus on the real and pernicious challenges impeding the development of effective ALS therapies, namely, the desperate need for a real understanding of disease mechanisms to allow for the development of effective treatments; (2) supplying investigational therapies, especially those unproven to have tangible improvements for patients, is beyond the NIH mission to advance our fundamental knowledge to improve health; (3) programs supplying investigational drugs have the potential to drive patients away from enrolling in placebo-controlled trials that are desperately needed to actually produce new and effective treatments for ALS patients; and (4) few small businesses would qualify for the program as defined by the statute, thus limiting the diversity of the investigational drugs that could be in the grant program. The final amended legislation addressed some of NIH's concerns by requiring entities to conduct research enrolling patients ineligible for other ALS clinical trials. However, NIH's principal concerns still hold true, and we strongly emphasize that investments in mechanistic disease research and therapy development are critical for the breakthroughs needed to develop transformative therapies for ALS.

Regarding the research component of the expanded access provision in the ACT for ALS, we remain concerned that the expanded access data obtained from persons with ALS on whom there is no research-grade data preceding an intervention, and for whom there is not a matched control group (gender, age, time from onset, rapid vs. slow course, etc.) with which to compare is unlikely to yield valuable scientific information. Even in instances where some reliable data would be gleaned, the information is unlikely to be transformative or rapidly accelerate ALS research. Except for an investigational drug that is so potent that it stops progression, any other finding would be impossible to ascribe to anything other than chance. As section 2 of the ACT for ALS Act specifies that investigational drugs in the expanded access grant program are confined to those in phase 3 clinical trials, a highly potent therapy would be first identified in the randomized controlled phase 3 trial. As of the date of the hearing, NIH has begun implementing the expanded access grant program. A request for applications was published on May 12, 2022.¹⁰

NIH places a high priority on research that will lead to the development of interventions for ALS and has increased funding for ALS research from \$52 million in fiscal year (FY) 2016 to \$120 million in fiscal year 2021. This increase is primarily due to the rise in research on Alzheimer's disease and related dementias, which supports research on those mechanisms and conditions that cause both dementia and ALS, rather than reflecting an increase in research on ALS alone. In addition to a broad array of research projects to understand the genetic and environmental causes of ALS and to elucidate the cellular and molecular mechanisms by which the disease progresses, in fall of 2021 NIH funded four exciting projects¹¹ through the Accelerating Leading-edge Science in ALS (ALS2) initiative, part of the NIH Common Fund's Transformative Research Awards, which aims to dramatically advance our understanding of what triggers ALS and what drives the rapid progression of this disease. NIH is also supporting several large natural history and biomarkers studies to improve our understanding of the disease process and to identify biomarkers that will predict when people at risk for ALS might get the disease, which would allow them to begin treatment early, perhaps even before symptoms appear. NIH-

¹⁰ grants.nih.gov/grants/guide/rfa-files/RFA-NS-22-071.html.

¹¹ www.ninds.nih.gov/news-events/directors-messages/all-directors-messages/spurring-innovative-research-toward-als-cures-through-accelerating-leading-edge-science-als-als2.

supported preclinical research projects are testing a range of therapeutic targets and agents, including gene therapies and small molecule drugs, in experimental models of ALS, including animals or cells/tissues, to treat inherited and sporadic forms of ALS. Several promising industry-funded clinical trials are based upon NIH-supported basic and preclinical research findings.

NIH is preparing for the future of ALS research by initiating a strategic planning process to identify the highest priorities for research that will lead to the discovery of effective interventions for the diagnosis, treatment, management, prevention, or cure of ALS. The process is engaging researchers, clinicians, advocates, people affected by ALS, multiple NIH institutes, and other Federal agencies, and has multiple opportunities for the general public to contribute to the process. Draft priorities will be presented for public comment at a public workshop on October 26–27, 2022.¹²

QUESTIONS SUBMITTED BY SENATOR RICHARD C. SHELBY

Question. Dr. Tabak, the fiscal year 2023 budget request does not continue its support for the Undiagnosed Diseases Network as it graduates from the Common Fund. The University of Alabama at Birmingham runs the Undiagnosed Diseases Network in partnership with Harvard and it has been a valuable resource to which to refer challenging cases and also is a network of strong collaborators to help researchers tackle those cases. More than that, it is a national resource for Americans who have an undiagnosed disease or disorder with no other place to turn.

Why is there not a plan in place to retain the Network and its clinical sites around the country?

Answer. The Undiagnosed Disease Network (UDN) was always planned for 10 years—the maximum period of support for Common Fund programs. In Phase II of the program (starting in 2018), the UDN was tasked with developing a framework to continue its mission after expiration of Common Fund support, ensuring sustained clinical utility for decades to come. For the final year of the program, the National Institutes of Health (NIH) will provide supplements and extensions to the UDN extramural clinical sites, Coordinating Center, and some Cores to ensure that all participants accepted by the end of the ninth year are evaluated as the program transitions to a larger, self-sustained network. Some sites have committed to continue enrollment during this period, and NIH is exploring means to enable other sites to continue to enroll new patients as well. The intramural Undiagnosed Disease Program, housed within the NIH Clinical Center and currently supported as a UDN clinical site, will continue to receive support and oversight from multiple NIH Institutes and Centers (ICs).

Multiple NIH ICs released a notice of intent to publish a funding announcement to support a Data Management and Coordinating Center to provide infrastructure and research support for a new network of clinical sites. Clinical sites with the appropriate infrastructure, expertise, and resources needed to conduct the clinical evaluation and DNA sequencing of participants enrolled at their sites can apply for designation as a Diagnostic Center of Excellence. Diagnostic Centers of Excellence will have access to resources of the Data Management and Coordinating Center.

NIH is committed to the successful transition of UDN and welcomes the opportunity to work with Congress to identify the best path forward. NIH's long-term vision is to see an expanded Network continue to make important scientific discoveries while improving clinical practice for undiagnosed patients—regardless of geographic location or socioeconomic status.

QUESTIONS SUBMITTED BY SENATOR SHELLEY MOORE CAPITO

Question. I am pleased to be the lead sponsor along with Senator Reed of the Childhood Cancer STAR Act. As we know, cancer remains the most common cause of death by disease among children in the United States. By the age of 50, more than 99 percent of the children who survived their initial cancer diagnosis will have had a chronic health problem, and 96 percent have experienced a severe or life-threatening condition caused by the toxicity of the treatment that initially saved their life. Thanks to the STAR Act, the NCI has supported new research into improving the quality of life of childhood cancer survivors.

¹² www.ninds.nih.gov/about-ninds/strategic-plans-evaluations/strategic-plans/amyotrophic-lateral-sclerosis-als.

Could you advise the Committee on how much of the \$30 million Congress has provided for the STAR Act each year has been invested in this research and how many new research projects you have been able to support with the STAR Act fund?

Answer. The National Cancer Institute (NCI) appreciates your and Senator Reed's leadership, and the Subcommittee's continued support for childhood cancer research, including support for the Childhood Cancer STAR Act. Each year, the Subcommittee has appropriated \$2 million of the \$30 million authorization to support the Centers for Disease Control and Prevention (CDC) in their implementation of STAR Act provisions focusing on enhancing CDC cancer registry efforts (Section 102 of the Act). NCI has used the remaining \$28 million of STAR Act funding to support new biobanking research efforts (Section 101) and to continue to conduct and support survivorship research projects (Section 202), as well as evidence reviews focused on childhood cancer survivorship (Section 203) in partnership with the Agency for Healthcare Research and Quality (AHRQ). These initiatives are supported through a variety of mechanisms, including but not limited to new research grants. Efforts in each of NCI's three areas are summarized below.

1. Biobanking Projects:

NCI is committed to making progress for children and adolescents and young adults (AYAs) with cancer, survivors, and their families, and biobanking efforts have long been a part of this mission. In accordance with the goals of the STAR Act, NCI provided supplemental funding to the Children's Oncology Group (COG) Biobank in 2019 to support immediate enhancements. NCI subsequently funded six supplemental projects, which are listed below, starting in 2020 to bolster and expand the current programs. The supplements included projects to increase collection of diagnostic, relapse, and autopsy specimens, as well as specimens from childhood cancer survivors enrolled in NCI's Childhood Cancer Survivor Study (CCSS). Pediatric cancers are classified as rare cancers, and these efforts will increase sample availability to researchers and clinicians in an effort to advance research and improve patient outcomes, especially for children with the rarest cancer subtypes.

- Rare Tumor Populations Biobanking (COG):* For rare cancers for which COG does not have open clinical trials, tumor tissue collection options are limited. This program expanded in fiscal year (FY) 2021 and supports tumor tissue and blood collection for specific groups of patients for which current tumor tissue collection is lacking or inadequate, with priority for tumor types with high risk of treatment failure. This initiative also collaborates closely with the Childhood Cancer Data Initiative (CCDI) to analyze tumor tissue to obtain a clinically relevant molecular profiling through the CCDI Molecular Characterization Protocol. The data helps this Protocol support characterization of tumors for rare cancers, with an initial emphasis on Central Nervous System (CNS) tumors as well as soft tissue sarcomas.
- Tumor Specimens from Patients at Relapse (COG):* 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. One area of focus is the collection of relapse specimens from children with rhabdomyosarcoma.
- Rapid Autopsy Specimen Collection (COG):* NCI and COG continue to work with patient organizations to support rapid autopsy collection of tumor samples from children and AYAs who have died of their disease. Foundations and families within the pediatric brain tumor community have been leaders in such programs, and we hope 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 help other families.
- Pediatric MATCH Diagnostic Specimen Collection (COG):* This effort collects diagnostic samples for children and AYAs who have already submitted samples at relapse through NCI's Pediatric MATCH Trial and enables molecular characterization to identify the changes in gene mutations and gene expression that occur between diagnosis and relapse. This in-depth characterization aims to inform development of more relevant treatments.
- Biobanking I—Specimen Collection of Subsequent Cancers (CCSS):* The development of subsequent malignant neoplasms (SMN) is associated with significant morbidity and mortality for survivors of childhood cancer. The CCSS has prioritized collection of SMN somatic tissue specimens (tissue blocks, scrolls, slides) from survivors with confirmed cases of subsequent malignancies. The re-

sults help design treatment protocols and interventions that will result in an increase in survival, while minimizing harmful late effects. This research is also used to develop and expand programs for early detection and prevention of late effects in children and adolescent cancer survivors.

—*Biobanking II—Specimen Collection to Study Chronic Health Conditions (CCSS)*: This project will enhance the CCSS as a resource for future biologic and genetic evaluations to better understand the causes of chronic health conditions in survivors of childhood cancer.

Many of the STAR Act supplement projects are still collecting samples and have contributed to many new NCI research projects. Childhood cancer researchers have requested and used biospecimens from STAR Act funded supplement projects for 11 new research projects, with 10 of these projects supported by NCI (in addition to the STAR Act investments described here) and one supported by the Cancer Prevention and Research Institute of Texas. Biospecimens will continue to be available for researchers in the coming years with continued support. Along with increasing the number of greatly needed samples, these projects also address other concerns and barriers to biobanking and provide opportunities to mitigate these challenges. Through implementation of the STAR Act biobanking provisions, NCI continues to support progress towards better understanding pediatric cancers. Additional details about each of these biobanking projects will be provided to Senators Capito and Reed, and their colleagues, in the biobanking report required in Section 101 of the STAR Act, which is anticipated to be transmitted to Congress in June 2022.

2. Survivorship Research Grants:

NCI also continues to conduct and support childhood and AYA cancer survivorship research that advances additional goals of the STAR Act. NCI issued a new request for applications (RFA) in March 2020, titled “Research to Reduce Morbidity and Improve Care for Pediatric, and Adolescent and Young Adult (AYA) Cancer Survivors” (RFA-CA-20-027/028), which builds upon a previous RFA, “Improving Outcomes for Pediatric, Adolescent and Young Adult Cancer Survivors” (RFA-CA-19-033), to continue to address survivorship research areas emphasized in the STAR Act.

NCI funded seven projects in response to RFA-CA-19-033 in fiscal year 2020, and 10 projects in response to RFA-CA-20-027/028 in fiscal year 2021. An additional final round of awards is expected to be finalized in the coming weeks. Commitments for these 5-year awards will extend to fiscal year 2026, pending availability of appropriations. Projects supported through the first two rounds of awards in fiscal year 2020 and fiscal year 2021 are described in more detail in the tables below.

These efforts aim to improve care and health-related quality of life for childhood and AYA cancer survivors, through mechanistic, observational, and intervention research projects that focus on six key domains: (1) disparities in survivor outcomes; (2) barriers to follow-up care; (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.

RFA-CA-19-033: Improving outcomes for Pediatric, Adolescent, and Young Adult Cancer Survivors	Tumor Types	Late/Long Term Effect(s)
Project Title, Principal Investigator, Institution, Grant Type		
Using Information Technology to Improve Outcomes for Children Living with Cancer ¹³ PI: Dr. Jin-Shei Lai (Northwestern University at Chicago), U01	All	Disease and treatment-related symptoms
A Randomized Trial of a Mobile Health and Social Media Physical Activity Intervention Among AYA Childhood Cancer Survivors ¹⁴	All	Sedentary behavior

PI: Dr. Nina Kadan-Lottick (Yale University), U01

Utility of Memantine in Preventing Cognitive Dysfunction in Children Receiving Cranial Radiotherapy ¹⁵ PI: Dr. Nadia Laack (Mayo Clinic), U01	Primary brain tumors	Cognitive dysfunction after cranial radiotherapy
A web-based patient-reported symptom monitoring and self-management portal for AYA breast cancer survivors ¹⁶ PI: Dr. Ann Partridge (Dana-Farber), U01	Breast cancer	Symptoms, unmet needs, concerns
Telehealth based exercise intervention to improve functional capacity in survivors of childhood cancer with significantly limited exercise tolerance ¹⁷ PI: Dr. Kirsten Ness (St. Jude), U01	All	Reduced exercise capacity, impaired physical dysfunction
An Interactive Survivorship Program to Improve Healthcare Resources [INSPIRE] for Adolescent and Young Adult (AYA) Cancer Survivors ¹⁸ PI: Dr. Karen Syrjala (Fred Hutchinson), U01	All	Emotional distress; adherence
Implementation of a Provider-Focused Intervention for Maximizing HPV Vaccine Uptake in Young Cancer Survivors receiving Follow-Up Care in Pediatric Oncology Practices: A Cluster-Randomized Trial ¹⁹ PI: Dr. Wendy Landier (University of Alabama), U01	All	Elevated risk of HPV-related complications and malignancies
RFA-CA-20-027/028: Research to Reduce Morbidity and Improve Care for Pediatric, and Adolescent and Young Adult (AYA) Cancer Survivors	Target Population	Topic Area
Project Title, Principal Investigator, Institution, Grant Type		
Predicting and Preventing Chemotherapy-Induced Cardiotoxicity in African American Children PI: Drs. Paul W Burridge and Yadav Sapkota (Northwestern University at Chicago), R01	African American, doxorubicin-treated childhood cancer survivors ²⁰	Cardiotoxicity
Bridging Information Divides and Gaps to Ensure Survivorship: The BRIDGES Randomized Controlled Trial of a Multi-level Intervention to Improve Adherence to Childhood Cancer Survivorship ²¹ PI: Dr. Nina S Kadan-Lottick (Yale University), R01	Childhood cancer survivors and primary care providers	Follow-up care
Social Genomic Mechanisms of Health Disparities Among Adolescent and Young Adult (AYA) Cancer Survivors ²²	Non-Hodgkin's lymphoma and Hodgkin's lymphoma survivors	Social determinants of health

PI: Dr. Bradley Jay Zebrack (University of Michigan at Ann Arbor), R01

SALSA—Study of Active Lifestyle Activation ²³ PI: Dr. Eric Jensen Chow (Fred Hutchinson Cancer Research Center), R01	Childhood cancer survivors	Cardiovascular disease
Individual, Cultural, and Area-Based Factors Associated with Survivorship Care Among Asian/Asian American Childhood Cancer Survivors ²⁴ PI: Drs. Kimberly Ann Miller and Joel E Milam (University of Southern California), R01	Asian and Asian American childhood cancer survivors	Follow-up care
Optimization of a mHealth Physical Activity Promotion Intervention with Mindful Awareness for Adolescent and Young Adult Cancer Survivors ²⁵ PI: Drs. Siobhan Marie Phillips and David Victorson (Northwestern University at Chicago), R01	Childhood and AYA cancer survivors	Quality of life
Pilot Test of an mHealth Intervention for Reducing Alcohol Use Among Rural Adolescent and Young Adult Cancer Survivors ²⁶ PI: Drs. Carolyn Lauckner and Laurie McIlouth (University of Kentucky), R21	Rural AYA cancer survivors	Alcohol consumption
Treatment-Specific Genetic Risk Scores for Late Effects Prediction in Childhood, Adolescent, and Young Adult Cancer Survivors ²⁷ PI: Drs. Cindy Im and Yan Yuan (University of Alberta), R21	Childhood cancer survivors	Risk for chronic conditions
Remote Monitoring of Cardiac Function in Childhood Cancer Survivors PI: Dr. Saro Armenian (Beckman Research Institute/City of Hope), R21	Anthracycline-exposed, long-term childhood cancer survivors ²⁸	Cardiac dysfunction
Caregiving for Young Adults with Cancer in Latino Families: Understanding Healthcare Engagement and Family Wellbeing ²⁹ PI: Dr. Michael A Hoyt (University of California-Irvine), R21	Latino AYA cancer survivors and their families and providers	Caregiving

¹³ reporter.nih.gov/search/owLPDXpgCU-iBbBTXwB1Qg/project-details/10247641

¹⁴ reporter.nih.gov/search/WCYrRYvZjUyxTUSKqGtHRA/project-details/10464453

¹⁵ reporter.nih.gov/search/hhFq_KlhjUK_3mrhwe8lzw/project-details/10020353

¹⁶ reporter.nih.gov/search/6iqMWMtbbk2QCXUdJKPvVw/project-details/10079364

¹⁷ reporter.nih.gov/search/vDZlwK9vOkCEXKq0gt1xIA/project-details/10075046

¹⁸ reporter.nih.gov/search/ouCqFYfadUaDvFDHKRpQvQ/project-details/10080015

¹⁹ reporter.nih.gov/search/JL500raCfUSRsLG_1qNHUg/project-details/10076219

²⁰ reporter.nih.gov/search/tuBqAK_RUKcGDcJFdrNqg/project-details/10275329

²¹ reporter.nih.gov/search/tuBqAK_RUKcGDcJFdrNqg/project-details/10274932

²² reporter.nih.gov/search/tuBqAK_RUKcGDcJFdrNqg/project-details/10272690

²³ reporter.nih.gov/search/tuBqAK_RUKcGDcJFdrNqg/project-details/10285925

²⁴ reporter.nih.gov/search/tuBqAK_RUKcGDcJFdrNqg/project-details/10275095

²⁵ reporter.nih.gov/search/SzDDxi0b_UWciL8xp_2iEw/project-details/10278744

²⁶ reporter.nih.gov/search/tuBqAK_RUKcGDcJFdrNqg/project-details/10273171

²⁷ reporter.nih.gov/search/tuBqAK_RUKcGDcJFdrNqg/project-details/10273416

²⁸ reporter.nih.gov/search/tuBqAK_RUKcGDcJFdrNqg/project-details/10274206

²⁹ reporter.nih.gov/search/tuBqAK_RUKcGDcJFdrNqg/project-details/10269806

3. *Childhood Cancer Survivorship Evidence Reviews, with AHRQ:*

NCI entered into an Inter-Agency Agreement with AHRQ to support its work to implement Section 203 of the STAR Act, focused on identifying best practices in survivorship care, through AHRQ Evidence Reviews on Childhood Cancer Survivorship. A summary of the progress is provided below.

4. *Disparities and Barriers to Pediatric Cancer Survivorship Care:*³⁰

This report was posted on the AHRQ website for public comment in October 2020, with simultaneous peer review. The final report was published in March 2021. The NCI used the findings of the report to provide funding through administrative supplements for the “NCI P30 Cancer Center Support Grants” to support research to understand and address organizational factors that contribute to disparities in outcomes among childhood cancer survivors (supported by NCI in addition to STAR Act investments). Additionally, this report has already begun to inform the broader cancer survivorship research community and survivorship care providers based on dissemination of the review findings.

5. *Models of Care That Include Primary Care for Adult Survivors of Childhood Cancer:*³¹

This report was posted on the AHRQ website in June 2021 for public comment, with simultaneous peer review. The report was published in February 2022. NCI and AHRQ are widely disseminating this report to raise awareness of the role that primary care providers play in the care of adult survivors of childhood cancers. NCI also plans to use the findings of this report to evaluate its current grant portfolio, to identify and assess potential gaps and opportunities for additional research on this topic.

6. *Transitions of Care from Pediatric to Adult Services for Children with Special Healthcare Needs:*³²

The systematic review is anticipated to be posted on AHRQ’s website in May of 2022. Similar to the other two reports, AHRQ and NCI expect to widely disseminate this report to the research community and the general public once it can be publicly posted to raise awareness of challenges in transitioning care from pediatric to adult services for children with special healthcare needs. This report is expected to serve as a resource for those with interests related to a number of serious healthcare diseases and conditions including cancer. The NCI also plans to use the findings of this report to evaluate its current grant portfolio, to identify and assess potential gaps and opportunities for additional research on this topic.

QUESTIONS SUBMITTED BY SENATOR PATRICK LEAHY

Question. The COVID–19 pandemic has adversely affected clinical cancer care and profoundly impeded progress in the provision of essential clinical trials for cancer patients, with rural populations particularly hard hit. Vermont is currently one of seven states eligible for the NIH Institutional Development Award (IDeA) that does not have an NCI-designated facility. Therefore, Vermont has faced reduced access to cancer clinical trials relative to more urban areas. Because access to clinical trials directly correlates with improved quality of cancer care, this reduced access leads to poorer outcomes for Vermonters diagnosed with or at risk for developing cancer. Many of these IDeA states that lack NCI-designated centers have medical schools that would be capable of conducting clinical trials.

How will the NIH better support cancer care and clinician investigator training in predominately rural IDeA states that lack an NCI-designated cancer center?

Answer. The National Cancer Institute (NCI) leads, conducts, and supports cancer research across the nation and is committed to helping all people live longer, healthier lives. Ensuring equitable access to cancer care and clinical trials across the country is a top priority for NCI. This objective was also recently reaffirmed as one of the goals identified in the next phase of the Cancer MoonshotSM, which includes NCI efforts to continue to support and enhance enrollment of underrepresented populations to cancer clinical trials, as well as cancer control research in persistent poverty areas.³³ In addition, NCI and the National Institute of General

³⁰ effectivehealthcare.ahrq.gov/products/pediatric-cancer-survivorship/research.

³¹ effectivehealthcare.ahrq.gov/products/childhood-cancer-survivorship-care/research.

³² effectivehealthcare.ahrq.gov/products/transitions-care-pediatric-adult/protocol.

³³ www.whitehouse.gov/ostp/news-updates/2022/03/17/fact-sheet-white-house-announces-initial-steps-for-reignited-cancer-moonshot/.

Medical Sciences (NIGMS) have recently issued several funding opportunity announcements (FOAs), discussed in more detail below, focused on promoting cancer research in rural communities, including communities in Institutional Development Award (IDeA) states and those that are not home to an NCI-designated cancer center.

NCI-designated cancer centers are a cornerstone of the NCI's cancer research efforts across the country, and many centers have large catchment areas that cross state lines. For example, the Dartmouth Cancer Center includes the entire states of Vermont and New Hampshire as part of its service area.³⁴ Greatly extending the reach of the NCI-designated cancer centers are several key extramural networks that support the majority of NCI-supported clinical trials: the National Clinical Trials Network (NCTN), the Experimental Therapeutics Clinical Trials Network (ETCTN), and the NCI Community Oncology Research Program (NCORP). The NCTN primarily conducts later-phase cancer treatment and imaging trials, while ETCTN conducts early phase cancer treatment trials. Research groups within these networks hold annual meeting sessions on topics related to underrepresented populations, and each of these groups has a patient advocate committee to provide input on developing and conducting trials. The ETCTN also recently launched the Create Access to Targeted Cancer Therapy for Underserved Populations (CATCH-UP.2020) program to enhance access via clinical trials to targeted cancer therapy for minority/underserved populations.³⁵

The NCORP includes 25 states with large rural populations³⁶ and expands the reach of the NCTN, bringing cancer research to people in their own communities. NCORP provides infrastructure for conducting studies on cancer control and prevention, cancer care delivery research, and screening, treatment, and quality of life evaluations embedded in treatment trials. The NCORP includes seven research bases and 46 community sites across the United States, including 14 minority/underserved community sites, and this locally based infrastructure includes approximately 1,000 component and subcomponent sites (e.g., hospitals, cancer centers, oncology clinics) through which patients can enroll in NCTN and NCORP clinical trials.

Even in IDeA states without NCI-designated cancer centers or NCORP grantees (such as Vermont, Rhode Island and West Virginia), NCI has active trial sites reaching rural patients. These sites are not required to have an NCORP grant or be associated with a designated cancer center to become a "member site" for an NCTN/NCORP group. Many academic sites are members even if they are not a designated cancer center, and community sites are eligible to be full members. These full member sites also have affiliated sites throughout the state or region where patients can be enrolled. In Vermont, for example, there are approximately 55 NCI-supported trials open to patients with a treatment site within the state,³⁷ and more than 230 Vermont patients enrolled in either NCORP or NCTN trials over the past 5 years. The top enrollment site was the University of Vermont Medical Center/College of Medicine in Burlington.

Clinicians from these NCTN/NCORP member sites can fully participate in the NCTN/NCORP groups, contribute to scientific development, and develop expertise in clinical investigations. Dozens of these investigators enrolled patients to NCTN and NCORP trials over the past 5 years, including more than 30 investigators with enrollments in Vermont and more than 60 investigators with enrollments in West Virginia. Investigator involvement in these NCI-sponsored programs provides critical opportunities for rural patients and produces valuable research findings. For example, Dr. Robert Ward of Rhode Island Hospital is a co-author on research showing that improved screening methods for women with dense breasts are needed because of their increased risk of breast cancer and of failed early diagnosis by screening mammography,³⁸ work that was funded by an NCORP breast cancer screening study.

NIGMS-supported research is also benefitting cancer patients in rural communities through IDeA Networks for Clinical and Translational Research (IDeA-CTR),³⁹ such as the Northern New England Clinical and Translational Research (NNE-CTR) Network,⁴⁰ which includes participating and collaborating healthcare,

³⁴ gis.cancer.gov/ncicatchment/.

³⁵ ctep.cancer.gov/initiatives/Programs/etctn_catch-up2020.htm.

³⁶ ncorp.cancer.gov/news/2019-08-19.html.

³⁷ clinicaltrials.gov/ct2/results?cond=cancer&term=&cntry=US&state=US%3AVT&city=&dist=&Search=Search&recrs=a&type=Intr&fund=0.

³⁸ doi.org/10.1001/jama.2020.0572.

³⁹ grants.nih.gov/grants/guide/pa-files/PAR-14-303.html.

⁴⁰ reporter.nih.gov/project-details/10205083.

educational and research institutions in Maine, Vermont, and New Hampshire. The IDeA-CTR awards support state-wide or multi-state regional networks of clinical and translational research, which build research infrastructure, develop investigators, and support research activities that address health conditions prevalent in populations of IDeA states. Since cancer affects individuals nationwide as well as in IDeA states, all 12 IDeA-CTRs invest in cancer research by supporting pilot research projects. These projects include mechanistic, translational, clinical, and prevention studies.

Recognizing that more research is needed to identify the best strategies for providing care to rural populations, NCI and NIGMS are currently providing funding for projects selected through three targeted FOAs:

1. Improving the Reach and Quality of Care in Rural Populations:⁴¹ This funding opportunity focused on strategies for delivering and improving the quality of cancer care in rural areas among low-income and/or underserved populations. Over the two funding rounds, nine research projects were funded, including research focusing on financial toxicity and navigation, survivorship, telehealth, community-based patient navigation for cancer screening, palliative care, and symptom management.

2. Social and Behavioral Intervention Research to Address Modifiable Risk Factors for Cancer in Rural Populations:⁴² This funding opportunity focused on research to develop, adapt, and test individual-, community- or multilevel interventions to address modifiable risk factors for cancer in rural populations. Three research projects have been funded after the first round, focusing on tobacco control in rural American Indian households, increasing physical activity, and utilizing telehealth options for treatment of obesity.

3. IDeA Clinical Research Resource Center:⁴³ Increasing the number of clinical trials and complex observational studies in IDeA states is a pressing need that requires continued efforts to strengthen clinical research capacity and maximize the use of existing resources through innovative approaches. The IDeA Clinical Research Resource Center (I-CRRC) funding opportunity aims to 1) strengthen communication and develop collaborations between health research institutions in IDeA states and clinical trial sponsors; and 2) develop clinical research coordinators with the knowledge and skills to manage clinical trials and complex observational studies.

NCI is committed to serving patients across the country, including those in rural areas who face disparities in incidence and mortality rates that can be attributed in part to barriers in accessing health services. NCI will continue to fund research and support efforts to improve access and better address the unique needs of these communities.

QUESTIONS SUBMITTED TO DR. ANTHONY FAUCI

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

Question. Dr. Fauci, there has been limited evidence that antiviral therapies to treat COVID-19, like Paxlovid, may relieve symptoms from long COVID. The theory is that long COVID may be caused by the virus persisting in parts of the body for months. What are your thoughts on this and what work is NIH doing in this space to determine if therapeutic treatments may relieve or even cure long COVID?

Answer. While most people recover quickly and fully from infection with SARS-CoV-2, some experience ongoing or new symptoms or other health effects after the acute infection has resolved, referred to as post-acute sequelae of SARS-CoV-2 infection (PASC). An understanding of the underlying mechanisms of PASC will be crucial as we work to identify and test therapeutics. The National Institutes of Health (NIH) supports research to inform estimates of PASC prevalence as well as to understand the pathogenic mechanisms underlying the wide range of observed symptoms and the risk factors for developing PASC. This includes the examination of whether particular symptoms associated with PASC may be caused by the persistence of virus or viral particles in parts of the body. NIH has launched the Researching COVID to Enhance Recovery (RECOVER) Initiative,⁴⁴ a trans-NIH effort that aims to understand, prevent, and treat the post-acute sequelae of SARS-CoV-2 infection. The NIH RECOVER Initiative complements ongoing studies supported by the National Institute of Allergy and Infectious Diseases (NIAID) to better un-

⁴¹ grants.nih.gov/grants/guide/rfa-files/RFA-CA-19-064.html.

⁴² grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-051.html.

⁴³ grants.nih.gov/grants/guide/pa-files/PA-22-150.html.

⁴⁴ <https://recovercovid.org/>.

derstand the various post-acute manifestations of COVID-19 and will engage more than 100 researchers at more than 30 institutions to build a diverse national study population and support large-scale studies in this critical area, as well as clinical trials of potential treatments for PASC. The knowledge gained through these collective efforts will help inform the identification of effective treatments for PASC, including those evaluated through RECOVER.

Question. How many clinical trials are funded by NIH that are testing treatments for long COVID?

Answer. The highly diverse symptomology of PASC observed in patients across the lifespan strongly suggests that PASC, rather than being a singular condition, is likely multiple clinical conditions that vary across the lifespan and demographic groups. This has important implications for the research approach to PASC—namely, multiple diverse diagnostic, treatment, and prevention strategies will be needed for the range of PASC conditions and patient populations. This will require an appropriately diverse portfolio of sufficiently scaled and powered clinical studies to generate high-quality data that can inform clinical and public health practices.

Toward this end, the NIH RECOVER Initiative, described above, is preparing to launch clinical trials to identify safe and effective treatments to enhance recovery of patients with persistent symptoms and identify interventions which, if initiated early, could prevent end-organ and systems damage and other sequelae. RECOVER has established a dedicated Clinical Trials Data Coordinating Center to implement and manage multiple interventions addressing symptoms/symptom clusters and underlying mechanisms of pathobiology of PASC. RECOVER also issued a solicitation for clinical trial proposals testing a range of interventions to address symptoms/symptom clusters and underlying mechanisms of pathobiology. RECOVER will test a variety of therapeutic strategies. The first trials are anticipated to be launched by the Fall of 2022. As understanding of underlying mechanisms leading to post-acute sequelae of SARS-CoV-2 infection improves through the RECOVER and other research activities, additional candidate interventions will be evaluated and selected for testing.

Question. How many of these trials are beyond a phase I trial?

Answer. The RECOVER Initiative plans to launch Phase IIb–III PASC clinical trials that leverage fit-for-purpose design strategies to maximize rigor, efficiency, and flexibility. Initial trials will likely focus on interventions that have shown promise in other recovery contexts and on current hypotheses regarding pathogenesis. As our understanding of underlying mechanisms leading to PASC improves through RECOVER and other research activities, additional candidate interventions will be evaluated and selected for testing.

Question. There have been recent reports of individuals taking Paxlovid, and then their symptoms return after their treatment is complete. Do you know why that may happen?

Answer. NIH scientists, in collaboration with the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA), are looking into possible ways to better understand the phenomenon of COVID-19 rebound after Paxlovid treatment. NIH currently does not have studies underway, but the agency is actively discussing potential studies to learn more about who this is affecting, how often it is occurring, and if a longer regimen would be more effective in certain cases. For additional information on what is currently known about the case reports of patients developing symptoms again after completing a course of Paxlovid, please refer to “FDA Updates on Paxlovid for Health Care Providers”⁴⁵ and the “CDC Health Alert Network Health Advisory on COVID-19 Rebound After Paxlovid Treatment”.⁴⁶

Question. How much of the \$1.15 billion appropriated has been obligated?

How much of this funding has been obligated or committed for clinical trials?

Answer. In December 2020, Congress provided \$1.15 billion in NIH funding, available for obligation over 4 years, to support research into the long-term effects of SARS-CoV-2. With this funding, NIH launched Researching COVID to Enhance Recovery (RECOVER) in February 2021. As of May 17, 2022, \$674.5 million has been obligated. Of that amount, \$137 million has been obligated to the launch of clinical trials, including the establishment of the Clinical Trials Data Coordinating Center.

The remaining funding will be distributed during the final 2 years of the RECOVER Initiative to support outyear activities of these ongoing clinical research studies, including (but not limited to): longitudinal clinical follow up of adult and pediatric patients enrolled in the cohort studies, autopsy studies, central research

⁴⁵ <http://www.fda.gov/drugs/news-events-human-drugs/fda-updates-paxlovid-health-care-providers>.

⁴⁶ <http://www.emergency.cdc.gov/han/2022/han00467.asp>.

services, pathobiology research, mobile health platform, data repositories, clinical biospecimen collection and repositories, Electronic Health Record/Other Real World Data studies, as well as support for NIH management of the RECOVER initiative through specialized administrative and technical expertise.

Question. What work is NIH doing related to long COVID to address the most burdensome of symptoms or the most severe cases?

Answer. The National Institutes of Health (NIH) has designed and launched Researching COVID to Enhance Recovery (RECOVER),⁴⁷ a major research effort of national scale to improve understanding of Post-Acute Sequelae of SARS-CoV-2 infection (PASC), including Long COVID, and to inform the development of safe and effective diagnostic, treatment, and preventive strategies. RECOVER includes a longitudinal study designed to have inclusive and diverse participant enrollment that is representative not only of the U.S. population generally, but of the population of sub-groups most severely affected by coronavirus disease 2019 (COVID-19). RECOVER also includes electronic health records (EHR) studies of over 60 million patient records; a systematic and standardized autopsy study at scale; a mobile health platform to enable broader and deeper engagement of participants; pathobiology and mechanistic studies and development of animal models; and clinical trials. Importantly, RECOVER is patient-centered and engages patients at every level of the Initiative, from local studies to protocol development, to overall governance of the Initiative.

NIH RECOVER is preparing to launch clinical trials to test treatment and preventive strategies for Long COVID. This includes creating a portfolio of prioritized interventions that:

- Address symptoms/symptom clusters of high priority to patients
- Will test a broad range of interventions
- Address current nascent hypotheses regarding the pathogenesis of Long COVID
- Have sufficient scientific rationale, appropriate safety profiles, technical merit, and feasibility
- Would be available/accessible to most patients
- Are ready to launch in the short term

To identify which Long COVID symptoms have the highest impact on patients' quality of life, RECOVER is taking a broad consultative approach with engagement of patient, practitioner, and research communities. For example, both patient participants in the RECOVER longitudinal cohort studies and a national sample (non-RECOVER) of patients are periodically surveyed regarding their symptoms and the burden posed by them; and interviews and focus groups with highly affected communities and the RECOVER National Community Engagement Group and patient representatives are periodically conducted for in-depth insights into patient perceptions of the burden of Long COVID symptoms. The input from these engagement activities is informing RECOVER clinical trial design, including the selection of interventions, to ensure that RECOVER clinical trials address the most burdensome symptoms of Long COVID.

QUESTIONS SUBMITTED TO DR. GARY GIBBONS

QUESTIONS SUBMITTED TO PATTY MURRAY

Question. Our country has lost over a million people to COVID-19 and countless more have been infected by this virus. And people of color have faced the worst of this crisis. Studies show that people of color are more likely to be hospitalized for COVID, and while some recover quickly and completely, others have persistent symptoms that linger for months. That's why, in December 2020, we appropriated more than \$1 billion in supplemental funding for NIH to study long-COVID.

What updates can you share about NIH's RECOVER Initiative and what we have learned about long COVID and how it impacts different communities?

What are the challenges you're facing in terms of recruitment for RECOVER's clinical trials, and how is NIH ensuring that they have diverse representation?

Answer. The National Institutes of Health (NIH) launched the Researching COVID to Enhance Recovery (RECOVER) initiative to better understand and ultimately to prevent and treat the broad array of post-acute symptoms of SARS-CoV-2 (PASC), commonly called Long COVID. At the center of RECOVER is a longitudinal observational study that is currently recruiting adults and children from other ongoing studies of COVID, Long COVID clinics, and other cohorts—many of which

⁴⁷ recovercovid.org.

have a history of including people from communities disproportionately burdened by disease.

The RECOVER research initiative is meant to significantly expand both our knowledge about the full clinical spectrum of symptoms, long term outcomes, and underlying biology of Long COVID, as well as our ability to develop safe and effective therapeutic interventions. It funds multi-disciplinary biomedical, clinical, and epidemiological studies, many focused on untangling the complex social and biological factors that cause higher rates of hospitalization and Long COVID in communities of color.

RECOVER studies highlight diverse participation and community engagement, and include clinical trials, clinical studies that leverage cohort data and specimens, a patient registry, pathobiology studies, a mobile health platform, and electronic health record (EHR) studies. Clinical cohort institutions were selected for RECOVER studies that have a proven track record in reaching communities hardest hit by the pandemic. For example, RECOVER includes the Institutional Development Award (IDeA) clinical research network, which supports research in states that historically have had low levels of NIH funding. Their clinical coordinating center is one of the main hubs for the adult cohort study. In addition, a Research Centers in Minority Institutions (RCMI) program awardee is also serving as a hub for the study.

As of May 2022, NIH has enrolled more than 5,000 people and is close to RECOVER's target recruitment of 6,000. Participants are undergoing testing at 46 sites in 23 states, along with the District of Columbia and Puerto Rico. Twenty-seven percent of enrollees live in federally designated medically underserved areas. Thirty-six additional sites will come online before the end of 2022. The completion dates for reaching target enrollment are January 2023 for adults and May 2023 for children.

Other research efforts are helping to increase understanding of Long COVID. For example, a recent study published in *The Lancet Digital Health*,⁴⁸ describes how researchers used Artificial Intelligence (AI) technology to comb through an EHR database of more than 13 million people to identify characteristics of people with Long COVID and those likely to develop it.

While recruitment into the RECOVER longitudinal observational study is progressing steadily, researchers are facing challenges. Strong competition for people with biomedical research skills has hindered core and site hiring and led to delays in opening local sites and study implementation. The enrollment of study participants—including those who are currently infected with COVID-19, those with Long COVID symptoms, and those who were previously infected but show no Long COVID symptoms (to act as control cases)—is still challenging. Participating in studies, which may require taking time off from work, is an economic barrier. The recent decline in the number of cases of acute SARS-CoV-2 infection, milder symptoms associated with Omicron variants that make people less likely to seek medical attention, and the rapid expansion of home testing makes it difficult to identify and recruit acute cases. In addition, the extremely high transmissibility rates of recent variants means that many people have been re-infected, which reduces the ability to find people who have never been infected.

Increasing enrollment rates in communities disproportionately affected by SARS-CoV-2 infection is a critical goal for RECOVER; NIH is therefore monitoring the diversity of enrollment closely. One of the challenges is limited awareness in some communities about Long COVID. Another is establishing trust among people with a history of mistrust in the biomedical research establishment and the Federal Government. This impedes RECOVER's ability to establish sufficient enrollment in clinical studies that produce enough high-quality data to provide the evidence base necessary to guide clinical practice and public health policy.

The NIH Community Engagement Alliance (CEAL) Against COVID-19 Disparities initiative was launched to establish a research approach to ensure the participation of black and brown communities in vaccine research trials that were then underway.⁴⁹ CEAL now bolsters RECOVER recruitment by working with research teams in 21 locations across the country to address misinformation, foster trust in science and research, and ensure inclusive participation in NIH research. Strategies include local media and social media outreach, search engine optimization (SEO) tactics, local community outreach and education, and using SARS-CoV-2 testing programs and point-of-care settings as recruitment platforms. Through trusted mes-

⁴⁸ [www.thelancet.com/journals/landig/article/PIIS2589-7500\(22\)00048-6/fulltext](https://www.thelancet.com/journals/landig/article/PIIS2589-7500(22)00048-6/fulltext).

⁴⁹ covid19community.nih.gov/.

sengers in communities hit hardest by the pandemic, CEAL and its community partners are helping increase diversity in Long COVID research.

Question. Many patients with long-COVID have been diagnosed with a blood circulation disorder known as postural orthostatic tachycardia syndrome, or POTS. Symptoms associated with POTS include lightheadedness, fainting and an uncomfortable, rapid increase in heartbeat.

Has NIH determined the rough proportion of long-COVID patients whose symptoms include POTS?

Answer. Dysautonomia refers to a disorder of autonomic nervous system function. The autonomic nervous system controls many of the unconscious and involuntary bodily processes such as heart rate, blood pressure, and breathing. Postural orthostatic tachycardia syndrome (POTS) is a relatively common dysautonomia in which moving to an upright position can trigger an excessive increase in heart rate (tachycardia) and other symptoms such as light-headedness, shortness of breath, chest pain, and palpitations. Other common symptoms not necessarily linked to posture include headache, fatigue, exercise intolerance, and impaired sleep, digestion, and concentration. While the cause of POTS is unknown, low blood volume, dysregulation of the autonomic nervous system, autoimmunity, and viral infection may all play a role, each perhaps leading to distinct subtypes of POTS. It is likely that POTS has multiple underlying mechanisms resulting in subtypes of POTS that need to be identified and characterized.

Symptoms of the post-acute sequelae of SARS-CoV-2 infection (PASC) may overlap with those experienced by persons suffering with POTS/dysautonomia. Research on the biological causes of PASC and potential treatments pose a unique opportunity to possibly discover the key pathophysiology underlying several disorders suspected to be the sequelae of a viral illness in a significant subset of those affected, such as POTS/dysautonomia and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

The Researching COVID to Enhance Recovery (RECOVER)⁵⁰ Initiative seeks to better understand, treat, and prevent PASC, including Long COVID, and to understand how SARS-CoV-2 can lead to long-lasting and widespread effects such as fatigue, decline in some cognitive abilities, pain, sleep disorders, and dysautonomia, among others. RECOVER is a patient-centered study of national scale with diverse participation and community engagement. RECOVER has multiple scientific aims, including to understand the clinical spectrum and the biology underlying recovery over time, and to define distinct sub-phenotypes of Long COVID. It includes multiple sub-studies: longitudinal observational clinical cohort studies with thousands of diverse participants across the lifespan, ancillary clinical studies leveraging the cohort data and specimens, pathobiology studies, analyses of electronic health records, and clinical trials. We expect RECOVER studies will advance understanding of other conditions believed to be triggered by infection, which will include COVID-19 related cases of POTS/dysautonomia and ME/CFS. We also expect that RECOVER studies will reveal the proportion of Long COVID patients that meet the criteria for POTS/dysautonomia and ME/CFS. RECOVER study teams and oversight bodies include experts in those conditions.

What work is NIH supporting to understand the underlying causes of POTS?

Answer. The National Institutes of Health (NIH) has supported a wide range of POTS-related grants and currently funds research examining the autoimmune basis of POTS and the autonomic pathophysiology of POTS. In addition, NIH intramural researchers are investigating possible associations between PASC and POTS/dysautonomia⁵¹ through comprehensive testing of the extended autonomic system in patients experiencing PASC.

At the direction of the Senate Appropriations Committee, the National Institute of Neurological Disorders and Stroke (NINDS) and the National Heart, Lung and Blood Institute (NHLB), with participation by Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), jointly convened a workshop in July 2019 to discuss the state of the science and gaps in the current understanding of POTS. NINDS and NHLBI prepared and submitted a Report to Congress⁵² based on workshop discussions between leading experts in POTS research and care, officials from the three sponsoring Institutes, and patient advocates.⁵³

⁵⁰ recovercovid.org/.

⁵¹ <https://reporter.nih.gov/project-details/10491027>.

⁵² https://www.nhlbi.nih.gov/sites/default/files/media/docs/NIH%20RTC%20on%20POTS_Final.signed.pdf.

⁵³ [chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.nhlbi.nih.gov/sites/default/files/media/docs/NIH%20RTC%20on%20POTS_Final.signed.pdf](https://www.nhlbi.nih.gov/sites/default/files/media/docs/NIH%20RTC%20on%20POTS_Final.signed.pdf).

In addition, in April 2021, NHLBI posted an article⁵⁴ about research in this field, and NINDS and NHLBI issued a Notice of Special Interest,⁵⁵ “Stimulate Research on the Diagnosis, Treatment, and Mechanistic Understanding of Postural Orthostatic Tachycardia Syndrome (POTS),” to encourage researchers to submit proposals designed to answer fundamental questions about POTS.^{56,57} The grant applications submitted in response to the Notice are currently under review, which evaluates the scientific and technical merit of research applications. NIH peer review process, which evaluates the scientific and technical merit of research applications.

In addition, NHLBI is leading an NIH-wide workshop on sex/gender-specific COVID-19 outcomes on June 16–17, 2022. The workshop will include a presentation and discussion of autonomic hemodynamic disorders, including POTS, in PASC and the need for better understanding of the underlying pathophysiology and development of specific treatment approaches. NIH continues to encourage investigator-initiated research grant applications on POTS.

QUESTIONS SUBMITTED BY SENATOR SHELLEY MOORE CAPITO

Question. Dr. Gibbons, I have a question about pulmonary fibrosis, or PF, a complex and deadly lung disease that affects over 250,000 people in the U.S. I am especially concerned about this disease because we have a lot of coal miners in West Virginia, and workers who are exposed to coal dust and silica are at higher risk of developing PF. Diagnosing this disease is complex, and by many estimates often takes over 2 years. In far too many cases, patients already have advanced PF by the time they receive a diagnosis.

What research is the NHLBI currently funding to address the serious problem of late diagnosis in PF?

Answer. Currently, Pulmonary Fibrosis (PF) has no cure, and for some forms of PF, such as Idiopathic Pulmonary Fibrosis (IPF), median survival is 3–5 years from diagnosis. Some studies show an association between coal and silica dust and the development of PF.

Current efforts by the National Heart, Lung, and Blood Institute (NHLBI) to address PF include the Institute’s Prospective Treatment Efficacy in IPF using genotype for N-acetylcysteine (NAC) Selection (PRECISIONS) study, a five-year study aiming to enroll 200 IPF patients. PRECISIONS will use genetic testing to identify patients likely to respond to the antioxidant NAC. The first PRECISIONS clinical trial will explore the effectiveness of precision medicine for IPF. NHLBI recently funded a cohort of currently unaffected but at-risk individuals who have more than two close family members with PF, which could demonstrate how genetics and family exposure could affect risk disease risk.

The Lung Health Cohort, in partnership with the American Lung Association, follows 4,000 healthy millennials (aged 25–35) to identify early risk factors (e.g., lifetime air pollution, potentially noxious inhalation exposures) and signs of lung disease, including IPF, to allow earlier and effective intervention. In 2021, NHLBI-funded researchers identified gene expression signatures in the blood of PF patients. This research may reveal new therapeutic targets and help monitor and predict disease course.

NHLBI is supporting collaborative projects to establish a set of model systems that reproduce essential IPF disease-defining features to advance understanding of the IPF pathogen from onset through disease progression. These projects will also provide a platform for identifying and testing novel treatment therapies. By developing several model systems in parallel, scientists could identify common fibrosis pathways.

QUESTIONS SUBMITTED TO DR. JOSHUA GORDON

QUESTIONS SUBMITTED BY SENATOR PATTY MURRAY

Question. We understand NIMH is working to eliminate disparities in youth mental health by the year 2030.

⁵⁴ <https://www.nhlbi.nih.gov/news/2021/decoding-mysteries-postural-orthostatic-tachycardia-syndrome>.

⁵⁵ <https://grants.nih.gov/grants/guide/notice-files/NOT-HL-21-008.html>.

⁵⁶ <https://www.nhlbi.nih.gov/news/2021/decoding-mysteries-postural-orthostatic-tachycardia-syndrome>.

⁵⁷ <https://grants.nih.gov/grants/guide/notice-files/NOT-HL-21-008.html>.

What specific areas of research are needed in order for NIMH to meet this ambitious goal?

Answer. As detailed in the September 2021 National Institute of Mental Health (NIMH) Report to Congress “Addressing Youth Mental Health Disparities,” NIMH is prioritizing research to address and reduce mental health disparities among underserved and underrepresented youth by 2031. To meet this goal, NIMH will encourage a full and diverse range of research—including basic science, translational science, and services and implementation research—focused on addressing the needs of youth across race, ethnicity, culture, language, gender identity, sexual orientation, geography, and social determinants of health (e.g., education, economic stability, quality of housing, access to healthcare). These research efforts will aim to identify ways to decrease risk, increase resilience and protective factors, improve access to and utilization of high-quality evidence-based care, and improve outcomes of treatment and services among populations negatively impacted by mental health disparities.

NIMH previously published information about the research needs that guide the activities of NIMH Divisions, Offices, and Teams that support mental health disparities research across the lifespan.⁵⁸ Additionally, in December 2021, NIMH, the National Institute on Minority Health and Health Disparities, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) hosted an expert conference to further inform research efforts specifically on youth mental health disparities. This conference included a diverse group of expert panelists to assess the state of the science and the short- and longer-term research priorities related to improving mental health treatment, services, and outcomes for youth and adolescents from communities that experience health and related disparities.⁵⁹

Specific areas of research that NIMH aims to support include:

1. Understanding structural social determinants of mental health (e.g., housing instability, family income, community resources, neighborhood characteristics, work or school environments, and structural racism), how they can be modified, and how they drive risk of, resilience to, and protection from the development of mental illnesses.
2. Identifying and understanding contextualizing factors, including environmental and historical factors, their impact on biology, emotion, cognition, and behavior, and how they mediate mental health disparities.
3. Assessing how local, state, and Federal policies, laws, and regulations impact social determinants of mental health, mental health service delivery, and outcomes among youth from populations impacted by mental health disparities.
4. Characterizing variation in biological and genomic processes within and among diverse populations historically underrepresented in genetics research.
5. Conducting longitudinal studies and other research focused on understanding and measuring how childhood experiences confer resilience to or risk for mental illnesses and suicidal thoughts and behaviors in youth from populations impacted by mental health disparities.
6. Improving the specificity of biomarkers and the accuracy of culturally appropriate diagnostic assessments (including risk calculators) for youth from populations impacted by mental health disparities.
7. Developing and validating culturally appropriate preventive interventions, including systems-level approaches (e.g., in classrooms, schools, communities) for youth and parents from populations impacted by mental health disparities.
8. Optimizing existing evidence-based approaches to minimize bias in diagnosis and treatment, and to improve continuity of care and mental health outcomes for youth from populations impacted by mental health disparities.
9. Addressing co-occurring mental illnesses in youth with intellectual and developmental disabilities, including youth with intersectionality with other high-risk groups.
10. Improving the implementation and availability of mental health prevention and treatment interventions and services, as well as programs to support youth and family functioning, within youth-serving institutions (e.g., educational settings, community-based after-school programs, faith-based programs, child welfare programs, juvenile justice settings).
11. Using innovative assessment and analytic methods to examine sub-populations and low base-rate behaviors (e.g., death by suicide) and to address complex, multi-modal datasets.

⁵⁸ www.nimh.nih.gov/about/organization/od/odwd/nimhs-approach-to-mental-health-disparities-research.

⁵⁹ www.nimh.nih.gov/news/events/2021/2021-youth-mental-health-disparities-conference-identifying-opportunities-and-priorities-in-youth-mental-health-disparities-research-summary.

12. Developing, testing, and implementing prevention and treatment interventions that are relevant to communities impacted by health disparities across a broad range of ages (e.g., infancy through young adulthood).

13. Engaging collaborative teams that include community partners to ensure that the outcomes and interpretation of research reflect the priorities of the population participating in the research.

14. Developing targeted interventions by examining risk and resilience within populations impacted by youth mental health disparities.

QUESTIONS SUBMITTED TO DR. RICHARD HODES

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

Aduhelm Decision

Question. Dr. Hodes, I've been watching with interest, as I suspect you have as well, the decisions FDA and CMS have made regarding the new Alzheimer's treatment, Aduhelm. What are your thoughts about CMS' decision to require only patients in a clinical trial to receive the first approved Alzheimer's drug in more than a decade? And how does that decision affect other NIH Alzheimer's clinical trials?

Answer. The National Institutes of Health (NIH) notes that the decisions issued by the U.S. Food and Drug Administration (FDA) and Centers for Medicare and Medicaid Services (CMS) are regulatory decisions, and NIH defers to these agencies on such matters. To date, the impact of the aducanumab (the generic name for Aduhelm) coverage determination on NIH clinical trials has been minimal. NIH will continue to press forward with its robust and diverse research portfolio in the area of therapy development, building on the advancements we have achieved thus far. We will continue to evolve our understanding about Alzheimer's and to develop more ways to detect, treat, and prevent this disease.

Question. Perhaps what is most concerning about the decision CMS made on Aduhelm is that it impacts not only this specific treatment, but all other monoclonal antibody treatments coming down the pike. Can you address what this CMS decision means for the future of NIH's clinical trials process for new Alzheimer's treatments?

Answer. NIH notes that the decisions issued by FDA and CMS are regulatory decisions, and NIH defers to these agencies on such matters. These decisions underscore the need to further advance our knowledge and support a broad range of therapies for Alzheimer's and related dementias. In fact, nearly three-quarters of National Institute on Aging (NIA)-funded Alzheimer's and related dementias drug trials in early phases (phase I or phase II) are for targets other than amyloid proteins. NIH will continue to advance its robust and diverse research portfolio in therapy development, building further on the significant achievements thus far to effectively prevent, detect, and treat these devastating diseases.

Question. Dr. Hodes, I know you had initial concerns about how CMS' decision may pull patients away from other NIH clinical trials and toward an Aduhelm trial instead, simply so they could have access to the new drug. Has that fear been realized and how have you worked to combat it?

Answer. These concerns have not been realized. To date, the impact of the aducanumab coverage determination on NIH clinical trials has been minimal.

Overactive Bladder

Question. Dr. Hodes, overactive bladder affects more than 38 million Americans, and is more common with aging and in women. Recent studies on anticholinergic medications, which are commonly prescribed drugs to treat overactive bladder, have shown that these medications have a negative impact on cognition and may lead to the development of Alzheimer's disease and related dementia. Given the potential adverse impact on the nation's elderly that will only increase as our population ages, is NIA studying these medications or working collaboratively with other Institutes to determine the safety and efficacy of anticholinergic medications, and any association they may have with cognitive decline and Alzheimer's disease and related dementia?

Answer. Overactive bladder occurs when the bladder is triggered to empty at the wrong time, leading to a sudden urge to urinate that a person may have difficulty suppressing. The symptoms of overactive bladder include urinary frequency, urinary urgency, and urge incontinence.

The National Institute on Aging (NIA) supports studies on a range of issues related to the causes, prevention, and treatment of overactive bladder. This includes research on the safety of long-term use of anticholinergic medications commonly pre-

scribed to treat overactive bladder and the associated risk of cognitive impairment and dementia. For example, NIA is supporting a clinical trial testing whether discontinuing use of anticholinergics improves cognition and lowers the risk of Alzheimer's disease and related dementias.⁶⁰ NIA is also funding a clinical trial to test a mobile app that integrates a personalized anticholinergic risk calculator, targeted multimedia such as videos and blogs to educate users regarding anticholinergics, and a conversation starter to help a patient self-initiate ending anticholinergic prescriptions with a healthcare provider.⁶¹ This trial will explore the impact of the app on prescription anticholinergic exposure among older adults and on cognitive function and quality of life. Other research studies currently funded by NIA seek to assess severe adverse events associated with the interaction of cholinesterase inhibitors used to treat Alzheimer's with anticholinergic medications;⁶² test mechanisms of neurotoxicity from anticholinergics;⁶³ evaluate extended cognitive, urinary, and functional trajectories in older incontinent women without pre-existing dementia who use anticholinergic medication;⁶⁴ utilize a novel model to investigate anticholinergic drug induced dementia;⁶⁵ improve how older adults living with dementia, their caregivers, and clinicians make decisions about using anticholinergic medicines;⁶⁶ and test electronic health record-based tools that engage caregivers to help primary care providers reduce medication overload and deprescribe medications that can worsen cognitive burden in patients with mild cognitive impairment, Alzheimer's disease, and related dementias.⁶⁷ In addition, a recent NIA-supported study found that exposure to strong anticholinergics increased the risk of transitioning from normal cognition to mild cognitive impairment.⁶⁸ Another recent NIA-funded study that evaluated adverse outcomes of anticholinergic medicines in patients with dementia and overactive bladder⁶⁹ found an increased risk of mortality associated with non-selective antimuscarinic (a subtype of anticholinergic drugs) medications in older adults with dementia.⁷⁰

The National Institutes of Health (NIH) is committed to continuing to fund research to improve the lives of people living with overactive bladder and will continue to fund research towards prevention of cognitive impairment in this, and other, areas.

QUESTIONS SUBMITTED BY SENATOR SHELLEY MOORE CAPITO

Question. Alzheimer's disease has certainly been in the news recently. While, there is plenty to discuss on Adulhelm and decisions regarding its coverage, I am interested in the role it can play in moving the science forward.

What is on the horizon to better understand Alzheimer's disease and how we can prevent/slow its progression?

Answer. Thanks to the increased investment in Federal funding for Alzheimer's and related dementias, the National Institutes of Health (NIH) has been able to embark on an ambitious research agenda and continues to make significant progress in discovering approaches that may prevent, diagnose, and treat these complex diseases.

Understanding Alzheimer's and related dementias: Roughly 10 years ago, we knew of just 10 genetic areas associated with Alzheimer's disease, and 20 years ago, we knew of only 4. That number has grown to more than 70 associated genetic areas today. These advances are already informing new pathways for potential prevention and treatments. For example, NIH-supported research involving a Colombian family with more than 6,000 living members led to the identification of a gene variant that may protect against the development of Alzheimer's.⁷¹ Studies to understand how this gene and others may protect against Alzheimer's suggest new possibilities for treatment options, which NIH is exploring further.

⁶⁰ reporter.nih.gov/search/Shaj-qYerkm0U6DRn1S6tg/project-details/10129872.

⁶¹ clinicaltrials.gov/ct2/show/NCT04121858.

⁶² reporter.nih.gov/search/pZSsBABfW0K-DPFCtVqRcQ/project-details/10212709.

⁶³ reporter.nih.gov/search/Ggd69UkxpkGGqF5IAEfYrg/project-details/10168318.

⁶⁴ reporter.nih.gov/search/0lm26jQsukuQXix5r-QvGw/project-details/10343015.

⁶⁵ reporter.nih.gov/search/0lm26jQsukuQXix5r-QvGw/project-details/10258975.

⁶⁶ reporter.nih.gov/search/Ggd69UkxpkGGqF5IAEfYrg/project-details/9926791.

⁶⁷ reporter.nih.gov/project-details/10370471.

⁶⁸ www.ncbi.nlm.nih.gov/pmc/articles/PMC6036636/.

⁶⁹ reporter.nih.gov/search/-xMveMuhZUWqFIMIntQeIw/project-details/9377896.

⁷⁰ pubmed.ncbi.nlm.nih.gov/32026255/.

⁷¹ <https://www.nia.nih.gov/news/unique-case-disease-resistance-reveals-possible-alzheimers-treatment>.

In addition, NIH funds research beyond genetics to understand the biological mechanisms associated with dementia. For example, National Institute on Aging (NIA) intramural researchers have identified several biological pathways linked to abnormal brain metabolism in people with Alzheimer's disease and related dementias.⁷² These researchers also identified 15 promising candidate drugs that have already been shown safe and effective for other conditions and are screening these for potential use in treating dementia. By studying drugs approved by the Food and Drug Administration (FDA) for other conditions, researchers may be able to accelerate the drug discovery process for Alzheimer's and related dementias.

Diagnostics: In the early 2000s, researchers could only confirm an Alzheimer's disease diagnosis via autopsy. NIH support has been instrumental in developing ways to image and visualize aggregations of specific proteins like amyloid and tau—the hallmarks of Alzheimer's—in the brain, making a diagnosis possible in living persons. NIH continues to advance new, less invasive ways of detecting these proteins. For example, NIH small business innovation research funding helped researchers at C₂N Diagnostics validate the PrecivityAD™ test, a more affordable and less invasive alternative to traditional Alzheimer's tests like brain scans.⁷³ This blood biomarker test is now available to some doctors who are sending blood samples to C₂N's lab to analyze blood for amyloid. In May 2022, the FDA granted marketing authorization for the first test for the early detection of amyloid plaques using cerebrospinal fluid.⁷⁴ The clinical study of this test utilized cerebrospinal fluid samples made available by the Alzheimer's Disease Neuroimaging Initiative, a key component of NIH-supported Alzheimer's research infrastructure.

These tests are poised to transform Alzheimer's diagnostics and clinical trial recruitment. For example, because they can be done without the need for expensive PET scanners and radioactive diagnostic agents, they can be used in a much broader range of clinical settings, such as community health centers, thereby removing a potential barrier to participation in clinical trials.

Clinical Trials: In 2015, NIH funded 38 clinical trials to treat and prevent Alzheimer's and related dementias. In 2022, NIH is supporting more than 400 trials, approximately half covering dementia treatment and prevention, and the other half covering care interventions for persons living with these diseases.⁷⁵ The growth of NIH's clinical trial portfolio, which includes a diverse range of promising therapeutic approaches, is directly attributable to increased appropriations. In fact, the number of therapeutic targets for drug candidates in NIH-supported trials has more than doubled from 2015 to 2022. This is particularly evident in early phase (phase I or phase II) trials, where more than three-quarters of the drug trials currently supported by NIH are for targets other than amyloid proteins in the brain.

Some of these clinical trials will share results soon. The Exercise in Adults With Mild Memory Problems (EXERT) trial,⁷⁶ which tests the effects of aerobic exercise on cognition in adults with Alzheimer's, will report topline results in August 2022. In December 2022, the PEACE-AD trial,⁷⁷ which evaluates the drug Prazosin to treat severe agitation in adults living with Alzheimer's who require full-time caregiving, will share topline results. In addition, the DISCOVER Study⁷⁸ testing the drug Posiphen® in adults diagnosed with Alzheimer's is expected to report results late this year or in early 2023.

Prevention: We now know there are several risk and resilience factors that may play a role in the development of dementia. One example is blood pressure control. Recent NIH-supported studies showed that intensive high blood pressure control significantly reduces the occurrence of mild cognitive impairment, a precursor to dementia in some individuals. NIH has taken steps to share these findings with the public through efforts like the Mind Your Risks® campaign.⁷⁹

In addition, a recent analysis of data from two NIA-funded longitudinal study populations, the Chicago Health and Aging Project (CHAP)⁸⁰ and the Memory and Aging Project (MAP),⁸¹ found that adhering to a combination of healthy behaviors

⁷² <https://www.nia.nih.gov/news/nia-study-identifies-fda-approved-drugs-may-also-be-helpful-dementia>.

⁷³ <https://www.nih.gov/news-events/news-releases/nih-small-business-funding-boosts-alzheimers-science-advances>.

⁷⁴ <https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-new-test-improve-diagnosis-alzheimers-disease>.

⁷⁵ <https://www.nia.nih.gov/research/ongoing-AD-trials>.

⁷⁶ <https://clinicaltrials.gov/ct2/show/record/NCT02814526>.

⁷⁷ <https://clinicaltrials.gov/ct2/show/NCT03710642>.

⁷⁸ <https://www.clinicaltrials.gov/ct2/show/NCT02925650>.

⁷⁹ www.mindyourrisks.nih.gov/.

⁸⁰ www.alzrisk.org/cohort.aspx?cohortid=15.

⁸¹ www.alzrisk.org/cohort.aspx?cohortid=60.

was associated with a lower risk of Alzheimer's, including in individuals with genetic risk factors for the disease.⁸²

The behaviors included engaging in regular physical activity, avoiding smoking, practicing light-to-moderate alcohol consumption, eating a high-quality diet, and engaging in cognitive activities. Practicing four or all five of these behaviors was associated with up to a 60 percent reduction in Alzheimer's risk.

The finding that behavioral choices appear to have an impact on the development of Alzheimer's even in individuals with a higher genetic risk is encouraging in terms of the promise of nondrug therapies in the search for effective treatments. To this end, NIH continues to support research to identify the best ways to help prevent dementia, including more than 130 clinical trials on nondrug interventions like exercise, diet, and sleep.⁸³ NIH also supports research on how to help people adopt and sustain these healthy behaviors over a lifetime.⁸⁴

QUESTIONS SUBMITTED TO DR. NORA VOLKOW

QUESTIONS SUBMITTED BY SENATOR ROY BLUNT

Opioids Research

Question. Dr. Volkow, since fiscal year 2018, NIH has been provided \$500 million in dedicated funding annually for opioids and stimulant research. However, according to data released last week by the CDC, opioid overdoses continue to rise, with deaths up nearly 50 percent in the past 2 years. What research has NIH produced to move the needle on overdoses?

Answer. The National Institute on Drug Abuse (NIDA) shares your concerns about rising rates of drug overdoses and mortality. In the past few years, this crisis has been driven largely by increasing availability of potent synthetic opioids such as fentanyl and increases in combined opioid and stimulant use. NIDA supports robust multi-pronged efforts to stem the overdose crisis, including research on drug use and overdose prevention interventions, emerging patterns of substance use, harm reduction approaches, development of medications for opioid and stimulant use disorders, and the impact of coronavirus disease 2019 (COVID-19) on substance misuse and comorbidities.

Adolescence and young adulthood are periods of particularly high risk for drug initiation and the development of addiction. Through its prevention research portfolio and through the HEAL Prevention Initiative,⁸⁵ NIDA is developing and testing strategies to prevent drug use risk in youth overall and specifically to prevent opioid initiation, misuse, and use disorder, in populations including American Indian/Alaska Natives, youth with justice system involvement, and youth experiencing homelessness. This research will also address the sustainability and cost of these interventions. Through one project, researchers have developed a patient education program to prevent diversion of stimulants prescribed for attention-deficit/hyperactivity disorder.⁸⁶ Initial evidence showed reductions in patients' disclosure of their prescription to friends, their intent to share, and being approached to share.⁸⁷

In 2020, NIDA expanded its National Drug Early Warning System (NDEWS), which monitors patterns of drug use, morbidity, and mortality. By analyzing counterfeit pills seized by law enforcement, NDEWS established that such pills are a growing source of fentanyl.⁸⁸ This suggests that many fentanyl exposures are unplanned, and that overdose risk could be reduced with simple tools like fentanyl test strips (FTS). NIDA supports studies on FTS use and research to improve FTS technology. NIDA's Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs also support innovative technologies to surveil drugs in community wastewater to monitor changes in drug use as well as the emergence of new drugs. These tools are valuable for assessing the impact of prevention and treatment interventions and helping to tailor resource allocation.

⁸² pubmed.ncbi.nlm.nih.gov/32554763/.

⁸³ www.nia.nih.gov/research/ongoing-AD-trials.

⁸⁴ www.nia.nih.gov/research/blog/2021/12/tis-season-healthy-habit-research.

⁸⁵ heal.nih.gov/research/new-strategies/preventing-opioid-use-disorder.

⁸⁶ <https://reporter.nih.gov/project-details/9980049>.

⁸⁷ Molina BSG., Kipp, HL., Joseph, HM., et al. Stimulant diversion risk among college students treated for ADHD: Primary care provider prevention training. *Acad Pediatr.* 2020; 20(1): 119–127.

⁸⁸ Palamar, JJ., Ciccarone, D., Rutherford, C., et al. Trends in seizures of powders and pills containing illicit fentanyl in the United States, 2018 through 2021. *Drug Alcohol Depend.* 2022;1:234.

In alignment with the National Drug Control Strategy, one of NIDA's priorities is to expand research on harm reduction, which focuses on reducing the risk of overdose and other harms associated with drug use. Through the NIH Helping to End Addiction Long-term® (NIH HEAL Initiative®), NIDA is establishing a new network to develop, test, and implement harm reduction strategies and assess the impact of state and local harm reduction policies.⁸⁹ NIDA research is also evaluating the implementation of peer-based opioid overdose education, naloxone distribution, and social support interventions and their impact in African Americans⁹⁰ and veterans.⁹¹

Through its Clinical Trials Network (CTN), NIDA has helped create an arsenal of medications for opioid use disorder (MOUD) that are effective in reducing overdose. NIDA supported development of naloxone, and more recently, Kloxxado, a nasal spray containing high-dose naloxone that was approved by the U.S. Food and Drug Administration (FDA) in 2021.⁹² NIDA continues to fund research aimed at treating opioid and stimulant use disorders and overdose with nearly 90 compounds at various stages along the drug development pipeline, including longer-acting overdose reversal agents; and since 2019, NIDA's Pharmacotherapies Development Program has ushered twenty-four investigational new drug (IND) applications and eight IND exemptions through the FDA's IND process. One of the most promising preclinical projects underway is optimizing, characterizing, and testing the efficacy of a novel compound for reversing opioid-induced respiratory depression involving fentanyl and fentanyl analogs, alone and in combination with methamphetamine.⁹³ Researchers are also studying the unique physiological and pharmacological effects of co-intoxication with fentanyl and methamphetamine in animal models and testing the ability of CS-1103 to normalize these effects.⁹⁴ Unfortunately, NIDA-funded research also shows that MOUD are underutilized.⁹⁵

NIDA funds research to overcome barriers to MOUD use in diverse settings, including prisons and jails. For example, one recent study found that 6 months after Rhode Island implemented a comprehensive OUD screening and treatment program at its corrections facilities, the state saw a 12.3 percent reduction in fatal overdoses overall and a 60.5 percent reduction among the recently incarcerated.⁹⁶ With support from the NIH HEAL Initiative, the HEALing Communities Study⁹⁷ and the Justice Community Opioid Innovation Network (JCOIN)⁹⁸ are expanding research efforts to increase MOUD use; test the effectiveness and adoption of new prevention interventions and medications; and together, use real-world evidence to address the needs of vulnerable populations.

Stimulant misuse and overdose, primarily involving methamphetamine, have also continued to rise and often co-occur with opioid misuse. Unlike the case for OUD, there are no clinically proven medications for methamphetamine use disorder (MUD), but NIDA has supported progress on this front. Recent findings from a clinical trial demonstrated that treating MUD with naltrexone, a type of MOUD, in combination with bupropion, an antidepressant with stimulant effects, for six weeks helped patients reduce their meth use and improved other symptoms, such as depression⁹⁹ (Trivedi, et al. 2021).

NIDA-funded research also helped establish that contingency management (CM) is effective for reducing misuse of opioids, stimulants, and other substances; in CM, patients are given incentives for reducing their drug use or engaging in treatment. NIDA funding led to the first FDA-authorized mobile apps for intended to help increase retention in outpatient treatment programs for SUD.¹⁰⁰ These cognitive behavioral therapy apps are intended to be used in conjunction with CM and other tools and strategies to reduce drug craving. Ongoing studies seek to improve these

⁸⁹ RFA-DA-22-046: HEAL Initiative: Harm Reduction Policies, Practices, and Modes of Delivery for Persons with Substance Use Disorders (R01 Clinical Trial Optional).

⁹⁰ https://reporter.nih.gov/search/pXhkeRP_10CxXi3NjmRQig/project-details/10354090.

⁹¹ https://reporter.nih.gov/search/pXhkeRP_10CxXi3NjmRQig/project-details/10298478.

⁹² https://reporter.nih.gov/search/pXhkeRP_10CxXi3NjmRQig/project-details/10298478.

⁹³ <https://reporter.nih.gov/search/Zmse6nG00kKHYseah5M4qw/project-details/10227069>.

⁹⁴ https://reporter.nih.gov/search/51gwUKe_70eDNuM13Y1IOQ/project-details/10433799.

⁹⁵ Xu, KY., Mintz, CM., Presnall, N., et al. Comparative Effectiveness Associated With Buprenorphine and Naltrexone in Opioid Use Disorder and Cooccurring Polysubstance Use. *JAMA Netw Open*. 2022 May 2;5(5).

⁹⁶ Green TC., Clarke, J., Brinkley-Rubinstein, L., et al. Postincarceration Fatal Overdoses After Implementing Medications for Addiction Treatment in a Statewide Correctional System. *JAMA Psychiatry*. 2018 Apr 1;75(4):405–407.

⁹⁷ <https://heal.nih.gov/research/research-to-practice/healing-communities>.

⁹⁸ <https://heal.nih.gov/research/research-to-practice/jcoin>.

⁹⁹ <https://pubmed.ncbi.nlm.nih.gov/33497547/>.

¹⁰⁰ <https://peartherapeutics.com/products/reset-reset-o/>.

apps and apply them in new ways, such as at-home initiation of MOUD (3R44DA042652).¹⁰¹

While these advances are moving the needle, the COVID-19 pandemic has exacerbated the overdose crisis. Nearly 15 percent of U.S. adults initiated or increased substance use to cope with pandemic-related stress,¹⁰² and drug overdose rates among adolescents doubled during the pandemic, after a decade of stability.¹⁰³ While Federal drug regulatory and healthcare agencies implemented policy changes to expand treatment access for people with SUD, pandemic restrictions still caused disruptions in treatment.¹⁰⁴ NIDA has supplemented many of its studies and programs during the pandemic, including the Adolescent Brain Cognitive Development SM Study (ABCD study®), to better understand the risks of pandemic-related substance misuse and identify possible ways to intervene, and to evaluate the impact of pandemic-related policy changes.

Question. During the COVID-19 pandemic, NIH stepped up and embraced the sense of urgency by creating programs like RADx, which was a Shark Tank-style program to develop more COVID tests. How can we incorporate that model into the urgent needs related to the opioid epidemic?

Answer. Addressing the addiction and overdose crisis requires innovation, and often, those in a position to develop solutions are not even aware of their potential to help. Therefore, NIDA uses the Federal government's small business innovation research (SBIR) and small business technology transfer (STTR) programs and novel, fit-for-purpose, funding authorities to help biotech startups develop innovative solutions that translate addiction science into healthcare and consumer products.¹⁰⁵

Under the statutory authority of the America Creating Opportunities to Meaningfully Promote Excellence in Technology, Education, and Sciences (COMPETES) Reauthorization Act of 2010, NIDA's annual "\$100,000 for Start a Substance Use Disorders (SUD) Startup" is a Shark Tank-style challenge that supports research ideas that are intended to be the foundation for the development of successful new startups.¹⁰⁶ Each year, this challenge provides ten winners with \$10,000 each and technical mentoring from NIDA biomedical entrepreneurship experts. This enables the winners to test the premise that their research idea can be fostered into a biotech startup that will eventually contribute to the pool of innovative small businesses that can successfully compete for NIDA's SBIR and STTR funding. Sound Life Sciences and Prapela were discovered and selected through this challenge. Sound Life Sciences used this award to build a startup around a novel app that turns a user's smartphone into a portable respiratory monitor capable of detecting changes in breathing associated with an overdose. If an overdose is detected, it will sound an alarm, provide instructions, and summon emergency services to the user's location.¹⁰⁷ Prapela developed a hospital bassinet pad that delivers gentle, random vibrations to treat newborns who were exposed to opioids before birth. The bassinet pad may help improve newborns' breathing and heart rate and may also be useful in infants with breathing issues due to premature birth.¹⁰⁸

Other innovative products grew out of the NIDA Market Fair, a Shark Tank-style funding solicitation strategy. NIDA staff pitched ideas for potential funding concepts to "Sharks" who were experts in product development and policy from other NIH Institutes and other Federal agencies. The best ideas were rapidly selected and developed into funding opportunities for small business applications. The Shark Tank-style selection of concepts for development assured that there was a need and a market, which, in turn, attracted the companies best suited to develop specific products. Biobot Analytics developed a wastewater testing and analysis method to detect community exposure to opioids that can inform local opioid response efforts; this company was also able to pivot and provide critical data on the presence of SARS-

¹⁰¹ <https://reporter.nih.gov/project-details/10153370>.

¹⁰² Czeisler, ME., Lane, RI., Petrosky, E., et al. Mental Health, Substance Use, and Suicidal Ideation During the COVID-19 Pandemic—United States, June 24–30, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(32):1049–1057.

¹⁰³ Friedman, J., Godvin, M., Shover, CL., et al. Trends in Drug Overdose Deaths Among US Adolescents, January 2010 to June 2021. *JAMA.* 2022;327(14):1398–1400.

¹⁰⁴ Meadowcroft, D. and Davis W. Understanding the Effect of the COVID-19 Pandemic on Substance Use Disorder Treatment Facility Operations and Patient Success: Evidence From Mississippi. *Subst Abuse.* 2022;16:11782218221095872.

¹⁰⁵ <https://nida.nih.gov/research/nida-research-programs-activities/nida-challenges-program>.

¹⁰⁶ <https://nida.nih.gov/research/nida-research-programs-activities/nida-challenges-program/2021-start-sud-startup>.

¹⁰⁷ <https://www.soundlifesci.com/>.

¹⁰⁸ <https://www.prapela.com/>.

CoV-2 in communities.¹⁰⁹ AppliedVR developed RelieVRx™, an FDA-authorized virtual reality-based tool to treat people with chronic low back pain by helping them learn how to better cope with pain.¹¹⁰

The goal is to reduce the need for opioids for many different pain indications and reduce the associated risk of developing an opioid use disorder (OUD). Workit Health® is an app that uses video chat and messaging technology to bring trained experts directly to those with SUDs via a phone or computer.¹¹¹ The company is working to develop a chat bot to improve patient engagement and is continually working to expand its services to treat additional disorders and co-occurring conditions. Woebot, developed by Woebot Health™, is a smartphone-based mental health chatbot intended to use artificial intelligence and language processing technology to deliver personalized cognitive behavioral therapy for people with SUDs.¹¹² Woebot is being expanded for use in additional mental health indications. In addition, We the Village provides online support for families or friends of someone who is struggling with substance use or has a SUD.¹¹³ The online support includes a course that aims to teach people communication and support skills and an online Q&A to help people share what they've learned, with the overall aim of helping loved ones reduce substance use and get treatment. These and other innovative products developed through NIDA support demonstrate that pairing sound science with biotechnology entrepreneurship has great potential benefit for those with addiction or at risk for overdose.

QUESTIONS SUBMITTED BY SENATOR SHELLEY MOORE CAPITO

Question. The release last week of the preliminary 2021 overdose statistics was a grim reminder of how much work we still have to do. Last Friday, I spoke with a mother who had recently lost her daughter to fentanyl laced methamphetamine. She shared that while the first responders had tried to use Narcan, since meth was the primary drug in her system it was ineffective.

How is research progressing for an overdose reversal drug similar to Narcan for meth/stimulant overdoses?

Answer. Unprecedented increases in drug overdose deaths in the last 8 years have been driven mainly by fentanyl, alone and in combination with other drugs. Co-involvement of stimulants in fentanyl-involved overdose deaths as well as increases in overdose deaths involving stimulants without any opioids are particularly concerning the National Institute on Drug Abuse (NIDA).¹¹⁴ The rate of methamphetamine-involved overdose deaths increased by 810 percent from 2013 to 2021, and the rate of cocaine-involved overdose deaths increased by 398 percent.¹¹⁵ There are currently no U.S. Food and Drug Administration (FDA)-approved medications to treat stimulant use disorder or stimulant overdose, but NIDA research is underway to better characterize stimulant overdoses and to develop treatments for overdoses involving stimulants, alone or in combination with opioids.

Researchers have developed an antibody against methamphetamine (IXT-m200) that binds the drug in blood and keeps it from entering the brain in animal models and is safe for use in healthy humans. As a next step, NIDA is funding a study in emergency department patients with methamphetamine intoxication to test the efficacy of the antibody in alleviating methamphetamine overdose symptoms.¹¹⁶ NIDA-funded researchers have developed a small molecule (CS-1103) intended to act like a sponge and clear drugs from the body; they are testing its ability to clear either fentanyl¹¹⁷ or methamphetamine.¹¹⁸ Researchers are also studying the unique physiological and pharmacological effects of co-intoxication with fentanyl and methamphetamine in animal models and testing the ability of CS-1103 to normalize

¹⁰⁹ <https://biobot.io/>.

¹¹⁰ <https://www.relievr.com/>.

¹¹¹ <https://www.workithealth.com/>.

¹¹² <https://woebothealth.com/new-rct-shows-woebot-reduced-problematic-substance-use-occasions-by-one-third#:~:text=In%20short%3A%20Woebot%20significantly%20reduced%20substance%20use%20occasions,a%20total%20score%20of%20%3E%2F%3D%20on%20the%20CAGE-AID%29.>

¹¹³ <https://wethevillage.co/>.

¹¹⁴ <https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates>.

¹¹⁵ cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm.

¹¹⁶ <https://reporter.nih.gov/search/Zmse6nG00kKHYseah5M4qw/project-details/10269933> (5U01DA053043).

¹¹⁷ <https://reporter.nih.gov/search/Lv70TeON70-p34mvyTTKXg/project-details/10390959> (2R44 DA052957).

¹¹⁸ https://reporter.nih.gov/search/ufTgufCYka3Auu_FIsAng/project-details/10425422 (5U01DA053054).

these effects.¹¹⁹ Other research underway is a preclinical project to optimize, characterize, and test the efficacy of a novel compound for reversing opioid-induced respiratory depression involving fentanyl and fentanyl analogs, alone and in combination with methamphetamine.¹²⁰

In addition to the studies described above, NIDA is currently supporting research on nearly 90 compounds aimed at treating opioid and stimulant use disorders and overdose at various stages along the drug development pipeline. NIDA also issued funding opportunity announcements to solicit additional research to develop new medications to prevent and treat stimulant use disorders and overdose co-involving opioids and stimulants,¹²¹ to develop pharmacotherapeutics and other medical therapeutic and diagnostic devices for opioid use disorder and stimulant use disorders,¹²² and to understand the mechanisms underlying the toxic effects of using opioids and stimulants together.¹²³

SUBCOMMITTEE RECESS

Senator MURRAY. And this committee will next meet in Dirksen 138, Tuesday, May 24, at 10 a.m., for a hearing on the Biden Administration's Budget Request for the Department of Education.

The committee is adjourned.

[Whereupon, at 11:29 a.m., Tuesday, May 17, the subcommittee was recessed, to reconvene at 10 a.m., Tuesday, May 24.]

¹¹⁹ https://reporter.nih.gov/search/51gwUKe_70eDNuM13Y1IOQ/project-details/10433799 (3U01DA053054).

¹²⁰ <https://reporter.nih.gov/search/Zmse6nG00kKHYseah5M4qw/project-details/10227069> (5U01DA051373).

¹²¹ NOT-DA-22-049: Notice of Special interest (NOSI): Medications Development for Stimulant Use Disorders.

¹²² RFA-DA-23-021: Developing Regulated Therapeutic and Diagnostic Solutions for Patients Affected by Opioid and/or Stimulants use Disorders (OUD/StUD) (R43/R44—Clinical Trial Optional).

¹²³ NOT-DA-20-007: Notice of Special Interest (NOSI): Preclinical and Clinical Studies of the Interactions of Opioids and Stimulants.