Attachment—Additional Questions for the Record

Subcommittee on Health
Hearing on
"The Path Forward: Advancing Treatments and Cures for Neurodegenerative Diseases"
July 29, 2021

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Responses to the questions are accurate as of the date of the hearing.

The Honorable Nanette Barragán (D-CA)

1. What does the BRAIN initiative mean for patients who are living today with neurodegenerative diseases, including diseases like Alzheimer's, Parkinson's, and ALS?

   Response: The goal of the Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative is to develop and apply innovative technologies to understand how brain circuits work and what goes wrong in disease. In keeping with the remarkable advances and new opportunities outlined in the BRAIN Initiative 2.0: From Cells to Circuits, Toward Cures report,[1] the BRAIN Initiative is actively investing in the development of transformative tools and data resources to explore the brain in ways previously beyond reach, providing unprecedented opportunities to develop new treatments and cures. The progress made by the BRAIN Initiative Cell Census Network[2] in creating atlases—comprehensive resources describing the structure, composition, and interactions among brain cells—of brain cell types across species has enabled researchers to define, for example, what goes wrong in specific human brain cell types that are particularly vulnerable in diseases such as Alzheimer's. These single cell analysis techniques from the BRAIN Initiative are revolutionizing the study of almost all neurodegenerative disorders. This discovery and others like it set the foundation for developing targeted therapies to treat, prevent and ultimately cure human neurodegenerative diseases.

   Ultimately, the BRAIN Initiative will provide the foundation of knowledge necessary to reduce the enormous burden of brain diseases, including neurodegenerative diseases like Alzheimer's, Parkinson's, and Amyotrophic Lateral Sclerosis (ALS), as well as a number of psychiatric disorders by developing circuit therapies. For example, support from the BRAIN Initiative has enabled researchers to develop brain-computer interface (BCI) devices capable of interfacing with the brains of people with ALS or other neurologic conditions, injury, or limb loss to restore their communication, mobility, and independence. The Initiative also funds several projects to test or optimize deep brain stimulation (DBS) therapy in people with Parkinson's Disease. These include projects to

[1] braininitiative.nih.gov/sites/default/files/images/brain_2.0_6-6-19-final_revised10302019_508c.pdf
[2] nature.com/immersive/d42859-021-00067-2/index.html

develop self-adjusting (known as "closed loop") DBS that have the potential to reduce treatment side effects, to improve freezing of gait (a symptom of Parkinson's), and to improve sleep in people with Parkinson's. BRAIN Initiative funding also is moving DBS therapy out of the lab and into the home setting with wireless recording of brain activity and adaptive stimulation, which helps to ensure that DBS is optimized for each individual.

2. The Biden Administration has proposed creating the Advanced Research Projects Administration for Health (ARPA-H). How might ARPA-H advance neurodegenerative disease research and how will your institutes collaborate with the new agency?

   Response: The proposed structure for the Advanced Research Projects Agency for Health (ARPA-H) is intended to empower the ARPA-H leadership and staff to set and execute on research priorities for a variety of high-risk, high-reward, milestone-driven projects that can lead to novel capabilities, platforms, and resources that are applicable to a range of diseases, including neurodegenerative diseases such as Alzheimer's disease and others.

   ARPA-H will provide an opportunity to build upon many principles the National Institutes of Health (NIH) employed when launching the BRAIN Initiative. With the ambitious goal of mapping the human brain, the BRAIN Initiative set up goals and milestones for transformational research in two ways: first, in providing detailed information that is not only a static map of cell types but also an encyclopedia of neuronal activities which will be a springboard for a generation of neuroscientists working on a host of diseases and conditions; and second, by investing robustly in developing new imaging and other technologies that can give scientists access to biological processes never before seen or measured, many of which will transform other areas of biomedical research.

   ARPA-H projects will emphasize cross-cutting technologies with wide applications across diseases, including neurodegenerative diseases like Alzheimer's disease, to maximize the impact on patient outcomes. While ARPA-H will have a distinct culture as an independent agency within the NIH, the expectation is that the ARPA-H can leverage NIH's infrastructure and expertise, and collaborate closely with NIH's Institutes, Centers, and Offices (ICOs) within the NIH enterprise to advance innovative health research.

3. Dr. Hodes, Alzheimer's disease has a disproportionate burden on communities of color. However, these communities are often underrepresented in clinical trials used to evaluate possible treatments. What strategies is the National Institute on Aging using through your Alzheimer's Disease Research Centers to make outreach efforts to minority and underserved communities a priority?

   Response: The National Institute on Aging (NIA) funds Alzheimer's Disease Research Centers (ADRCs) at major medical institutions across the United States. Researchers at

these centers are working to translate research advances into improved diagnosis and care for people with Alzheimer's disease and Alzheimer's disease related dementias (AD/ADRD), as well as to find ways to treat and possibly prevent these diseases. The ADRC network has long been one of the cornerstones of NIH's AD/ADRD research infrastructure and employs a number of strategies to reach underserved communities to increase participation in AD/ADRD studies.

In 2020, NIA added four new exploratory centers to the ADRC network. The new centers are enhancing research initiatives with underrepresented populations, such as Black/African Americans, Native Americans, and those in rural communities, and expanding the network's reach into new geographic areas. Each exploratory center is designed to address regional health disparities. In Las Vegas, researchers are collecting high-quality standardized clinical data from people in rural settings, and in Nashville, they focus on vascular risk factors among Black/African Americans. The Albuquerque center prioritizes rural communities, particularly American Indians, and in Birmingham, the focus is on people in this Deep South region, especially Black/African Americans.

In 2021, NIA added two new ADRCs, in North Carolina and Texas, that will expand the network's reach and enhance collaborative studies with diverse populations. The centers are bolstering research on early and midlife risk factors for AD/ADRD and research to understand and help diminish the burden of these diseases on groups both underrepresented in biomedical research and disproportionately affected by dementia, specifically Mexican Americans and Black/African Americans, which are among the fastest growing older populations in the United States. The North Carolina center will focus on identifying age-related changes across the lifespan that impact the development, progression, and experience of AD/ADRD. The center will also identify how factors that arise in early and midlife contribute to racial, ethnic, and geographic disparities in dementia. The Texas center will harness its unique geographic location in South Texas — a region of approximately 5 million underserved Mexican Americans — to build connections with the community and enhance the diversity of data and biosamples available through the national network of ADRCs.

To enhance efforts to promote diversity of research participants, the ADRC network has established a Latino interest group that includes a listserv for Latino researchers and those with an interest in research with Latino participants and issues specific to Spanish language assessment. This group is helping to ensure that materials are available in Spanish, addressing the needs of Spanish-speaking participants, and ensuring that research capacity exists for assessment in Spanish. In addition to Spanish, assessments at ADRCs have also been translated into Chinese. In collaboration with the ADRC Latino interest group, NIA has developed a new website landing page as a portal to aging-related health information content and information on participating in research in Spanish.

Each ADRC also has an Outreach, Recruitment and Engagement Core that interacts with its local community, works with NIA and non-governmental organizations to promote awareness of Alzheimer's and related dementias among the public as well as clinicians, develops informational and research materials, and contributes to the Alzheimer's and

Dementia Outreach, Recruitment, and Engagement Resources (ADORE), a repository of materials to support recruitment and retention of participants into clinical trial and studies, including materials specifically designed for a variety of underrepresented groups in AD/ADRD research. ADORE includes recruitment plans, videos, toolkits and guides, brain donation resources, research articles, and more.

The ADRC network remains committed to improving outreach to underserved communities to ensure that all people will benefit from advancements in AD/ADRD studies.

4. My mother is one of millions of Americans suffering from Alzheimer's disease, so this is not theoretical for me, it's very real, day to day living. On behalf of those patients, and the families that are supporting them, I'm wondering what we in the federal government can do to help find a cure.

    a. Do you think that if the federal government treated these neurological diseases as public health crises, and gave them a name like Operation Stop Alzheimer's, and attached a timeline and funding goal to them like we did with Covid, that that would help yield concrete results?

    Response: AD/ADRD are among the greatest public health challenges of this century, and millions of families and communities experience the heartbreaking impact of these diseases on a daily basis. NIH has been able to invest more heavily in research on AD/ADRD leading to tangible progress. The NIH's continued significant investment in this research indicates our recognition of this public health crisis and the urgency with which the NIH strives to address it and realize the vision of a world in which dementia can be prevented, people at risk can be tested before dementia symptoms develop, and those with dementia can be treated so that symptoms are prevented or much delayed. NIH funding of AD/ADRD research has increased 4.5-fold since 2015 to meet the urgency of this challenge. We will continue to diligently pursue successful interventions, tools, and support for people living with dementia and for their families and other care partners.

    In 2012, the Department of Health and Human Services did give a name to a national strategy to address the public health crisis associated with these conditions, the National Plan to Address Alzheimer's Disease. This plan set a goal of preventing and effectively treating these devastating diseases by 2025. Recognizing the urgency of this goal, the NIH has developed a set of research implementation milestones that lay out the steps and accomplishments needed to achieve that goal. These milestones are developed with the input of stakeholder communities and are assessed and updated annually to ensure that appropriate steps are being taken and progress is being made. Each year, the NIH Professional Judgment Budget for Alzheimer's Disease and Related Dementias proposal outlines the resources needed to advance NIH-supported research closer to the 2025 goal through progress on these research milestones.

NIA appreciates the continued support from Congress, that has allowed the institute to advance the pace of research to effectively prevent, detect, and treat AD/ADRD. We are much closer now to living in a world in which these conditions do not take the enormous toll they do today.

b. What else can we do to increase the urgency needed to find a cure?

Response: According to a recent NIH-funded analysis, an estimated 6.25 million Americans are now living with Alzheimer's disease. The estimate increases to about 12.7 million Americans with Alzheimer's in 2050 and to more than 13.8 million in 2060. Deaths from AD/ADRD are a leading cause of mortality in the United States. The population of Americans aged 65 and older is projected to grow from 58 million in 2021 to 88 million by 2050. As the size of the U.S. population aged 65 and older continues to increase, the number of Americans with Alzheimer's or other dementias will grow, and the costs will also increase. In 2010, the costs of treating these diseases were projected to fall between $159 and $215 billion. By 2040, these costs are projected to jump to between $379 and more than $500 billion annually. This does not include $256.7 billion in unpaid caregiving by family and friends. These statistics highlight the urgency of finding effective treatments for AD/ADRD.

Increased messaging and public outreach of these staggering statistics can help communicate the urgency of this issue. NIA continues to disseminate information through www.alzheimers.gov and its Alzheimer's Disease and Related Dementias Education and Referral (ADEAR) website portal. The ADEAR Center is the primary federal government resource for free information about AD/ADRD research, participation in clinical trials, and caregiving. The ADEAR Center educates the public about the latest research findings and provides evidence-based information online, in print, and via a call center. NIA disseminates ADEAR's resources through outreach in the research and care communities and through media and advocacy organizations via weekly e-alerts, and social media outreach. NIA also provides information through www.alzheimers.gov, a newly enhanced website designed to educate and support people whose lives are touched by AD/ADRD. In September 2021, NIA launched a Spanish language version of www.alzheimers.gov. The website serves as a federal government portal for dementia information and resources. In addition, NIA provides information through its website, infographics, presentations, promotion of materials from the Alzheimer's and Dementia Outreach, Recruitment, and Engagement platform (ADORE, an online database of materials on topics related to the engagement, recruitment, and retention of participants in AD/ADRD studies), and collaboration with other federal agencies and advocacy organizations.

c. Do we need to focus on building our understanding of underlying disease biology, or do we need to strengthen the regulatory and reimbursement systems to

incentivize investment, including ensuring appropriate reimbursement for innovative diagnostics that are critical to identify the right patients for clinical studies, or is it some combination of all these things?

Response: AD/ADRD are complex disorders caused by a cascade of molecular events in the brain. From a research perspective, yes, we need to further develop our understanding of the underlying disease biology. The NIA has funded, and is continuing to invest in, novel and innovative research to identify the genes, proteins, and cellular mechanisms that contribute to the disease process, and that might be leveraged to interfere with it. Recent scientific breakthroughs, such as those in genetics, have demonstrated success with this broad approach. Continued NIH investments in research to identify underlying biological mechanisms, such as the role of inflammation, that cause these diseases will be critical to the future discovery and development of potential drugs targeting those processes.

Many researchers are now exploring whether AD/ADRD treatments should be approached using a "personalized medicine" strategy, like cancer, in which different types of dementia will likely require targeted treatments aimed at an individual's unique disease characteristics.

Lab and imaging tests that are available now, along with others in development, should enable clinicians in the future to diagnoses subtypes of AD/ADRD with significantly increased specificity. To this end, the NIA also invests heavily in research to develop less expensive testing methods and innovative diagnostics to allow earlier diagnoses and more accurate identification of patients for clinical studies, including blood and plasma biomarkers, other types of biomarkers, and cognitive screening assessments. The NIA also supports research to understand how health system organization and payment practices influence access to care, utilization, and health outcomes as well as how these factors drive health disparities. Together, this research can inform policy to improve care and treatment for all Americans.

5. We know that there are equity issues and health disparities that must be addressed when it comes to neurogenerative diseases. For example, Black and Latinx individuals are disproportionately affected by Alzheimer's disease and other dementias and are also more likely to face obstacles to timely diagnosis, enrollment in clinical trials, and access to adequate care following a diagnosis. What steps can be taken to ensure diverse populations have broader access to, and better representation in, clinical trials? When it comes to coverage and payment policies for existing diagnostics, how can those be improved to ensure broader access to care? Is the recently introduced FIND Act a step in the right direction?

   Response: To ensure that prevention and treatment interventions will be effective for all people with AD/ADRD, investigators must recruit and engage research participants from more diverse populations, including Blacks/African Americans and Hispanics/Latinos, who are at higher risk of dementia than white Americans. NIA is coordinating,

collaborating, and funding a range of activities to ensure that diverse populations have broader access to and representation in clinical trials, including the following past and ongoing activities:

- In 2018, NIA released the *National Strategy for Recruitment and Participation in Alzheimer's and Related Dementias Clinical Research* developed in collaboration with the Alzheimer's Association and other stakeholders. The National Strategy outlines practical, proactive approaches to help study sites engage a wider, more diverse number of volunteers. It focuses on four overarching themes: increasing awareness and engagement nationally; building and improving capacity and infrastructure at study sites; engaging local communities and supporting participants; and developing an applied science of recruitment. As part of the implementation of this strategy, NIA also released a Recruitment Planning Guide which has detailed information and concrete steps with guidance and checklists to help research teams.
- In 2018, NIA released a funding opportunity announcement (FOA) focused on "Examining Diversity, Recruitment, and Retention in Aging Research." Through this FOA, NIA supports research projects focused on improving the research tools, methods, and recruitment practices used in clinical studies to produce a significant number of committed research participants in aging research.
- In 2019, NIA launched the ADORE repository, a searchable collection of resources related to the engagement, recruitment, and retention of diverse participants in dementia clinical trials and studies. Researchers, community advocates, and study coordinators can search the ADORE database to find materials and strategies to help recruit participants, including materials specifically designed for a variety of underrepresented groups in AD/ADRD research, including Asian Americans, American Indians, African Americans/Blacks, and Hispanics/Latinos. Some of these materials are available in Spanish and other languages.
- NIA continues to support the Alzheimer's Clinical Trials Consortium (ACTC), a clinical trials infrastructure to accelerate and expand studies for therapies in AD/ADRD. ACTC is investing in methods and strategies to enhance recruitment of racial and ethnic minoritized participants. One of the approaches focuses on community engagement, using an innovative hub-and-spoke model to create a core of community-based participant advocates who work closely with the recruitment units at ACTC sites. These advocates serve as liaisons between the community and the ACTC sites, communicating the concerns and perspectives of potential and enrolled study participants.
- NIA also continues to operate ADEAR, a current, comprehensive, unbiased source of information about Alzheimer's and related dementias. ADEAR manages the Alzheimers.gov clinical trials finder, which is a searchable database of clinical trials and studies related to AD/ADRD. ADEAR also offers resources and referrals to AD/ADRD clinical trials and information, in English and Spanish.
- NIA recently launched the Clinical Research Operations and Management System (CROMS), which provides the capability to track, report, and manage clinical research data from NIA grantees, including participant enrollment in supported studies, in near real time (monthly). The CROMS resource is enabling NIA and

its funded investigators to intervene early to assist with enrollment challenges and support recruitment and retention of underrepresented populations in AD/ADRD research.

- NIA also recently launched OutreachPro, an online research tool to help increase participation by traditionally underrepresented populations in clinical trials and studies on AD/ADRD. Outreach Pro enables those involved with leading clinical research to create and customize participant recruitment communications materials such as websites, handouts, videos, and social media posts tailored to diverse audiences and available in both English and Spanish.
- NIA is exploring the possible development of community-based research network resources, including practice-based research networks (PBRNs), to increase participation in AD/ADRD Clinical Trials. One goal of this resource development is to build the community infrastructure of NIH investigators and sites in traditionally underrepresented communities.
- NIA funded the Foundations of Representative Engagement, Valid, and Effective Recruitment (FOREVER) in Alzheimer's Research project in September 2020. Through this project, researchers are developing and implementing novel methods for recruitment, engagement, and retention of groups underrepresented in research into AD/ADRD studies through community engagement and the NIA-funded Alzheimer's Disease Research Centers. The research team is also developing recruitment, engagement, and retention metrics and interventions, and establishing communications frameworks to improve literacy for both the general public and research communities. Conducting clinical trials with participants who are not only representative of the broader U.S. population but also most affected by the disease, as well as helping the field better recruit diverse participants is a high priority for NIA, and we will continue to strongly pursue these important issues.
- NIA has provided funding to increase the numbers of African American/Black and Hispanic/Latino participants in two of the primary nationally representative data sources for tracking the incidence and prevalence of dementia as well as longitudinal trends in dementia risk factors in the US population: the Health and Retirement Study and the National Health and Aging Trends Study.

The NIA will continue to play a leadership role in the implementation of the National Strategy, working across NIH Institutes and other federal agencies as well as with relevant stakeholders and community partners. NIA will also continue to emphasize the need for careful and realistic planning for recruitment and retention of diverse participants in AD/ADRD studies, to support and disseminate research on effective strategies for study participation, and to conduct further targeted outreach and information distribution to increase awareness, all with consideration to language access needs. These efforts will help to ensure that diverse populations have broader access to, and better representation in, clinical trials for AD/ADRD research. NINDS also conducts strategic planning efforts to identify health equity research gaps and opportunities to address and intervene in disparate health outcomes in AD/ADRDs. As part of the NIH's annual research Summits that are responsive to the National Plan to Address Alzheimer's Disease, NINDS leads the ADRD Research Summit every three years. Now in the

planning stage for the 2022 ADRD Research Summit, prioritized research objectives focused on addressing health disparities will be refined and developed.

6. Dr. Hodes, it can be challenging to get early diagnoses of diseases such as Parkinson's, ALS, and Alzheimer's. Initial symptoms can be hard to detect and be misdiagnosed as part of natural aging. What kinds of research is the National Institute on Aging supporting to identify early detection methods that can allow for earlier interventions and treatment? How can Congress better support this research?

   Response: Identifying the earliest signs of AD/ADRD before substantial cognitive damage has occurred and employing earlier interventions to delay or halt disease progression are critical for helping those affected by these diseases and their families and other caregivers. Research is underway to better understand many aspects of screening and diagnostics for clinical and community settings, including how they work in diverse populations, how they relate to biomarkers, and the balance of potential harm from false positives with potential benefit from early and accurate diagnosis.

   As effective treatments for AD/ADRD become available, doctors will need reliable tests for early detection and diagnosis to allow for earlier intervention.

   NIA funding has enabled significant progress in developing, testing, and validating biomarkers for diagnosing these diseases and the further development of blood and imaging tests. For example, since fall 2020, physicians in clinical practice can now order a blood test for amyloid protein, a hallmark sign of Alzheimer's, for an individual who is not participating in a study. Several other blood tests are in development. Also, the U.S. Food and Drug Administration (FDA) approved the first PET scan product to detect tau tangles in the brain, which are another hallmark of Alzheimer's.

   However, the current ability to obtain an AD/ADRD diagnostic test in a doctor's office is still quite limited, and biomarker imaging and lab tests are mainly used today by researchers to study people who volunteer to take part in related studies. NIA continues to fund studies to discover and validate additional testing options. NIA invests in research on many blood biomarkers, such as amyloid, tau, and other proteins and lipids. In addition, NIA-funded research has made recent advances in identifying other types of biomarkers such as eye and vision changes and measures of sleep disturbances.

   At the same time biomarker tests are being developed to detect the earliest clinical signs of AD/ADRD. NIA and other National Institutes of Health (NIH) institutes are supporting researchers who are developing tests to detect cognitive changes and low-cost detection of cognitive decline. Of special interest are tools that are inexpensive, easy to use in the community, and culturally appropriate.

   - Researchers are expanding the reach of the NIH Toolbox® for Assessment of Neurological and Behavioral Function (originally funded by 14 NIH Institutes, Centers, and Offices) and adapting it for use on mobile devices and in the telehealth setting. Released in 2012, the tool provides clinicians and researchers with brief,

measures to assess motor, emotional, sensory, and cognitive performance from ages 3 to 85 years, with both English and Spanish versions available. Currently, the NIH Toolbox measures, or parts of the measures, are available in six additional languages. To date, more than 900 clinical studies are using the NIH Toolbox, and more than 350 peer-reviewed articles have been published. The NIA-supported Advancing Reliable Measurement in Alzheimer's Disease and Cognitive Aging (ARMADA) study is validating the NIH Toolbox measures for use with people with Mild Cognitive Impairment and early-stage Alzheimer's, including those from racially and ethnically diverse groups. Through this same effort, which leverages the ADRC network, researchers are validating NIH Toolbox in adults aged 86 and older.

- The Consortium for Detecting Cognitive Impairment, Including Dementia (DetectCID), a research effort led by the National Institute of Neurological Disorders and Stroke in collaboration with NIA, is developing, testing, and validating several novel cognitive impairment assessments that are simple and easy to administer in primary care and other everyday clinical settings. Scientists leading these research projects are dedicated to developing clinical tools that are culturally appropriate and effective across all populations. Now in phase 2, DetectCID is broadening the testing and validation of these assessments with a larger number of research participants— at least half of whom are from underrepresented racial/ethnic groups.
- Researchers recently reported the development and validation of a combination of tests to assess mild cognitive impairment. The combination of tests, which are being used in the NIH-sponsored EXERT clinical trial of exercise, measure thinking skills such as planning, working memory, time management, and organization.
- NIA anticipates that research funded in response to a 2017 Funding Opportunity Announcement (FOA), Mobile Monitoring of Cognitive Change, will also be informative to healthcare providers in the future. This FOA invited applications to design and implement research infrastructure that will enable the monitoring of cognitive abilities and age, state of disease, context, or health condition-related changes in cognitive abilities on mobile devices.

NIA has funded research to identify many other signs of cognitive decline, including analysis of writing samples to detect certain patterns of language, and monitoring financial data, financial decision-making capacity, and susceptibility to financial exploitation. For example, a study using Medicare and credit report data from over 81,000 Medicare beneficiaries in single-beneficiary households over a 20-year period found that individuals diagnosed with AD/ADRD experienced missed credit payments and subprime credit scores at a higher rate than those who did not develop AD/ADRD. Moreover, the increased proportion of financial difficulty was evident in missed credit payments 6 years prior to diagnosis and subprime credit scores 2.5 years prior to diagnosis. The proportion of financial difficulty persisted for at least 3.5 years after diagnosis.

In addition, ongoing research includes the development of other novel measures, including electronic health record- based tools, digital assessments of cognition and function, collected unobtrusively, that may help clinicians identify who is at higher risk, as well as brief measures that can be used by primary care providers or given to a close

associate or spouse of the person. These have been studied in diverse populations to help identify people with AD/ADRD.

Congress can help advance this research by spreading the word to constituents that participation in clinical trials and other research is critical to the development of preventive interventions and cures for these diseases. Sufficient numbers of people, including representation of individuals from diverse communities who are impacted by these diseases, are essential in clinical trials, to assure that treatments developed work in all people.

7. Some early research has associated SARS, MERS, and now Covid with long-term neuroinflammation & neurological damage. What research is NIH currently doing or funding to assess whether Covid is likely to cause an increase in the incidence of ALS or other neurodegenerative diseases like Charcot Marie Tooth?

   Response: In June, NIH launched the REsearching COVID to Enhance Recovery (RECOVER) Initiative,[3] which aims to rapidly improve understanding of why some individuals who have symptomatic COVID-19 don't fully recover (often called Long COVID) or develop new or returning symptoms after recovery. These conditions are referred to by the research community as post-acute sequelae of SARS-CoV-2 infection (PASC). RECOVER studies are expected to provide insights into many important questions including the incidence and prevalence of long-term effects from SARS-CoV-2 infection, the range of symptoms, underlying causes, risk factors, outcomes, and potential strategies for treatment and prevention. The RECOVER Initiative also hopes to answer whether SARS-CoV-2 infection triggers changes in the body that increase the risk of other conditions, such as brain disorders like ALS or other neurodegenerative diseases.

   In addition to RECOVER, which includes a clinical science core, data resource core, and biorepository, the National Institute of Neurological Disorders and Stroke funds the COVID-19 Neuro Databank-Biobank (The NeuroCOVID Project)[4] that is creating and maintaining a national resource documenting and studying neurological complications of COVID-19, as well as potential exacerbation of pre-existing neurological conditions. The Rare Disease Clinical Research Network (RDCRN) program[5] run by the National Center for Advancing Translational Sciences conducted a collaborative study to understand the impact of the pandemic on people with rare diseases. Responses from the RDCRN survey represented people with over 152 rare diseases, including ALS and Charcot Marie Tooth disease, and a follow up survey is currently being prepared. The "Clinical Research in ALS & Related Disorders for Therapeutic Development (CReATe)" Consortium,[6] part of the RDCRN, was an active contributor to survey data. Intramural research at NIH is also examining long term neurological symptoms associated with COVID-19.

[3] recovercovid.org/
[4] med.nyu.edu/departments-institutes/population-health/divisions-sections-centers/biostatistics/research/neuro-databank-biobank
[5] ncats.nih.gov/rdcrn
[6] reporter.nih.gov/search/YWOjGF3bfUC58fqnlUFRKg/project-details/10242880

8. Recently, NIH and Dr. Robert Brown of UMass identified a new genetic mutation that causes ALS: SPTLC1. This mutation predominantly impacts juveniles of African descent. What is the NIH doing to further research into this mutation?

   Response: The recent discovery of variants in the SPTLC1 gene as an ultra-rare cause of juvenile ALS in individuals of African descent, and also some Caucasians, was enabled through an international collaboration of ALS scientists, including scientists in the NIH Intramural Program and scientists supported by extramural NIH funding. The discovery was published in August 2021, and we expect to receive grant applications proposing to further analyze this intriguing discovery, including studies to define the precise cellular defects associated with this form of ALS and to identify potential therapeutic targets. Several NIH funding opportunity announcements are suited for such research, and previous and currently active NIH grants fund similar follow-up studies on other ALS gene discoveries

9. It is our understanding that the C9orf72 mutation originated with the Vikings and disproportionately impacts people of Norwegian descent; the SOD1 mutation disproportionately impacts people of Asian descent. What genomic studies has the NIH done or funded to study the prevalence of genetic mutations among Latinos, African Americans, Native Americans, and Americans of Indian descent? What percentage of NIH research dollars spent on ALS are spent on such diversity research?

   Response: Since 2014, NINDS and NCATS have jointly funded the "Clinical Research in ALS & Related Disorders for Therapeutic Development (CReATe)" Consortium,[7] part of the NIH Rare Diseases Clinical Research Network, that aims to advance the discovery and validation of biomarkers, improve understanding of the relationship between clinical phenotype (observable traits) and underlying genotype (DNA sequence), increase clinical trial readiness in ALS, and reduce potential patient barriers to participate in clinical research. CReATe is composed of over ten clinical sites across the US and several international sites. All US-based clinical sites of CReATe are enrolling individuals of minority populations diagnosed with ALS to identify and measure the prevalence of ALS gene mutations. In addition, an international site of CReATe in Cape Town, South Africa is specifically enrolling non-white Africans. Other genetic studies funded by NIH, including in the Laboratory of Neurogenetics in the NIA Intramural Research Program, also analyze DNA samples from individuals of minority populations diagnosed with ALS to identify ALS genetic mutations in minority populations. An unofficial estimate of NINDS FY 2020 funding shows that NINDS spent approximately $7.4 million on genetics research in ALS. Because genetic studies of minority populations are part of larger studies, it is not possible to accurately determine the exact funding for research on diverse populations.

10. As you are aware, a small percentage of ALS patients live beyond 10 years. What efforts has the NIH taken to study these long-term survivors to assess what OMICS or other

[7] reporter.nih.gov/search/YWOjGF3bfUC58fqnlUFRKg/project-details/10242880

factors may be contributing to their improved survival?

Response: Most people with ALS die within 3-5 years of diagnosis, but survival times are increasing due to improvements in symptomatic care of ALS through pharmacological and non-pharmacological interventions, as well as better adherence to treatment guidelines. In addition, a small number of patients like Stephen Hawkings live for decades with the disease. It is currently not known if these long-term survivors of ALS share specific biological features, but it is likely that multiple factors contribute to improved survival. Scientists funded through the intramural and extramural programs of the NIH are addressing this question, for example, by analyzing the association of specific ALS gene mutations with survival times. The field is also using machine learning methods to analyze ALS 'omics-type datasets in order to obtain insight into the variability of disease progression rates in ALS.

11. Acting Commissioner Woodcock has frequently spoken about how the "War on Cancer" and its concurrent increase in funding resulted in expedited research and treatments. She has suggested that neurodegenerative diseases need a similar "war." What percentage of ALS research applications receive grant funding? If you were the decision maker for a War on ALS, what amount of annual funding do you believe it would take?

    Response: The NINDS maintains a robust portfolio on research on ALS, with the goals of building further scientific understanding of the cellular and genetic mechanisms that give rise to this disease and translating these findings into more effective therapies for ALS patients.

    The NIH does not use predetermined targets for a specific disease area or research category and typically does not provide dedicated funding to any one type of disease. Rather, the NIH relies heavily on scientific peer review, in which highly trained outside scientists review research applications and judge them on factors such as scientific merit, potential impact, and likelihood of success. The amount of funding in any given areas is dependent on a number of factors, including the number of applications received; of those received, the number that are judged meritorious by peer review; and the overall level of appropriations that NIH receives in a given year.

    It is also important to note that basic research is vital to achieving progress in diseases for which little or no progress has been made. Decades of NIH investments have demonstrated the value of basic research as a foundation for clinical advances, even though this research may lack a direct initial connection to a specific disease. Basic research illuminates future directions for research on a variety of conditions, with advances often coming from unexpected scientific places.

    Finally, the NIH does not report the number of applications received in specific research areas, such as for ALS, and thus cannot determine the success rate for those applications. However, each year NINDS establishes a payline, which is a percentile-based funding cutoff point determined by balancing the projected number of applications with the amount of funds available. If an application receives an NIH peer review score that falls

within the payline, it is typically funded. It is important to note that the overall NINDS payline is the 14th percentile, and for neurodegenerative disorders that are classified as Alzheimer's Disease and Related Dementias, which includes some ALS projects, our payline is currently the 28th percentile.

12. Are you aware of how the suicide rate in ALS compares to the national suicide rate or the suicide rate for oncological diseases?

    Response: The National Institute of Mental Health (NIMH) is the lead NIH Institute for research on suicide and is not currently funding research on suicide among individuals with ALS or oncological diseases, but recognizes that individuals with chronic illnesses such as cancer, heart disease, or diabetes may be at higher risk for mental illnesses and suicide than individuals without chronic illnesses.

    Suicide is major public health concern. In 2019, suicide was the tenth leading cause of death overall in the United States claiming the lives of over 47,500 people. While suicide rates can be found on publicly accessible databases, such as the Centers for Disease Control and Prevention (CDC) WISQARS (Web-based Injury Statistics Query and Reporting System) and CDC WONDER (Wide-ranging ONline Data for Epidemiologic Research), it is difficult to determine whether a comorbid chronic illness, such as ALS or cancer, is linked to suicide in an individual. Although CDC WONDER makes it possible to search for multiple causes of death, the codes used to identify causes of death are highly specific. For example, one cannot search for "suicide" and "ALS" as multiple causes of death; you would need to know the method or final cause of death (e.g., respiratory failure) for each to determine the rates.

    In terms of research on suicide rates among individuals with ALS or oncological diseases, several studies cite suicide as a cause of death among patients with ALS, and the Veterans Administration has funded research that found that risk of death by suicide was higher among veterans with ALS than veterans who do not have ALS. A study from Denmark reported a 4.9-fold increase in suicide in those with ALS and Huntington's disease as compared to those without neurological disease.

    Suicide among individuals with cancer is an important research area. A recent study analyzed data from more than 8 million patients with cancer, and found that of these, 0.154 percent died by suicide. Additional analyses of this sample identified possible risk factors, such as age, gender, and type of cancer.

The Honorable Brett Guthrie (R-KY)

The U.S. has seven National Primate Research Centers funded by NIH, that constitute a network of unique research institutions that provide important scientific resources for advancing biomedical knowledge and improving human health.

1. In regard to research surrounding neurodegenerative diseases, how much of this research is conducted at the National Primate Research Centers? I see the Administration requested $50 million for the centers, but House appropriators denied it. Why do you think that is? In your opinion, would research and development of treatments and cures for these diseases be adversely impacted if the NIH did not fund these centers?

   Response: The National Institutes of Health (NIH) emphasizes the fact that animals in research are valuable resources that require appropriate care for and use of throughout the lifespan of research. Nonhuman primates in particular continue to be an essential research resource and have unique and specific needs and require appropriate infrastructure to ensure their welfare and the responsible conduct of research. The budget request for nonhuman primate infrastructure would cover facilities used to house nonhuman primates which require continual updates and maintenance to ensure responsible stewardship over these invaluable resources. The funds in the budget request would be distributed by soliciting applications from NIH grantees to make necessary improvements to existing facilities, not to establish new nonhuman primate facilities. Research has shown that specific parameters for housing not only improve animal welfare, but also research outcomes in terms of reproducible findings. In addition to ethically appropriate housing, nonhuman primates require a proper diet, clinical/veterinary care as well as psychological and environmental enrichment, which necessitates skilled staff and additional resources including supplemental produce, various enrichment devices such as foraging devices for food, various toys, and puzzles.

   NIH supports expansion at existing NIH-supported facilities to leverage the current investment, through the national consortium of seven National Primate Research Centers (NPRCs) and other breeding colonies that collectively address research needs and trends, best husbandry practices, maintenance of genetic diversity, standardization of models, ethics, rigor, and reproducibility. *All seven NPRCs include neuroscience as an area of emphasis*. NPRCs are national resources serving not only NIH-funded investigators but other federally funded investigators, foundations, and industry.

   NIH cannot comment on appropriations decisions, but is committed to the fact that research using animal models, including nonhuman primate models, has led to tremendous advances critical for saving countless lives and extending human life expectancy around the world. Robust infrastructure to ensure welfare and scientific outcomes is essential to the science we support, to achieve these aims, the NIH budget included investments in nonhuman primate facilities, resources, and enrichment. NIH will continue to conduct and support research in accordance with the highest scientific and ethical principles.