Attachment—Additional Questions for the Record

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

Walter J. Koroshetz, M.D., Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health

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

The Honorable Frank Pallone, Jr. (D-NJ)

1. What is the biggest barrier to identifying clear clinical outcomes in neurodegenerative diseases?

   Response: Several inter-related challenges impede our ability to understand, identify, and ultimately treat neurodegenerative disorders. There are many underlying and not yet fully understood biological processes that result in neuronal death and degeneration. These varied brain changes lead to a wide spectrum of symptoms and clinical outcomes. Adding to the complexity, different disease processes and related clinical outcomes often overlap especially in the elderly. The greatest progress is occurring in learning how strongly associated genetic risk factors cause neurodegeneration. There is also considerable excitement that these will be amenable to genomic therapies. Least well known are the environmental factors that drive the greatest population risk. Key to tackling this complexity is to develop an array of methods to connect underlying biological processes to resulting symptoms, in effect revealing various signatures of neurodegeneration that can inform individualized diagnosis and treatment. To this end, NIH places a large emphasis on developing and validating biomarkers of neurodegeneration, including those that can signal early, pre-symptomatic disease processes.

   The National Institute of Neurological Disorders and Stroke (NINDS) supports investigator-initiated biomarker projects in neurodegenerative diseases and also designs funding opportunity announcements (FOAs) to encourage research into high priority biomarker research areas. In response to recent FOAs, several new studies aim to develop and validate biomarkers for multiple sclerosis, Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease (PD), Alzheimer disease and Alzheimer's disease related dementias (AD/ADRDs), as well as several other forms of neurodegeneration. For example, a recently launched consortium is applying cryo-electron microscopy to visualize, at atomic-level resolution, the structures of protein aggregates found in several ADRDs to identify several targets for PET biomarkers, which could enhance differential dementia diagnosis and serve as markers of disease progression in future AD/ADRD clinical trials. One longer running program, started in 2012, is the Parkinson's Disease Biomarkers

Program (PDBP)[1], which aims to discover biomarkers for PD even before symptoms appear. To identify biomarkers that distinguish PD from other closely related diseases and improve our understanding of these diseases, NINDS has expanded PDBP to include atypical parkinsonisms (disorders that cause movement problems similar to those in PD), such as progressive supranuclear palsy and corticobasal degeneration, as well as related synucleinopathies, such as multiple system atrophy and Lewy Body Dementias (LBDs). This work has been integrated into the Accelerated Medicine Partnership in Parkinson's disease, a public private partnership to advance biomarker discovery. Additionally, the NINDS Biomarker[2] and the NIH NeuroBioBank programs[3] provide resources for discovering and validating biomarkers for all neurological disorders, including neurodegenerative diseases.

NINDS also supports several studies that are focused on linking biomarkers to symptoms and specific functional impairments, for example in cognitive and movement domains. Most elderly individuals diagnosed with Alzheimer's disease have concomitant cerebrovascular disease. In the vascular contributions to cognitive impairment and dementia (VCID) space, the newly launched "Diverse VCID" is a consortium supporting 27 investigators at 12 institutions to use MRI and other measures to determine how commonly occurring white matter lesions contribute to cognitive impairment and dementia, including synergy with common comorbidities. The project will leverage resources from the ongoing MarkVCID[4], which has developed several VCID biomarkers. Further, MarkVCID has moved into its second phase, which will test these biomarkers in a pragmatic clinical trial and rigorously validate the ability of these biomarkers to detect disease and measure disease progression.

The process of demonstrating a reliable link between the biomarker and clinical benefit, is crucial, but can often be lengthy, difficult, and expensive. As more rigorous, focused development and validation of biomarkers takes place, NIH aims to support a pipeline of biomarkers that can be used in therapeutic development programs, phase 2 clinical trials, and clinical practice. The studies described above represent just a few of the ongoing NIH-supported biomarker investments in neurodegenerative diseases.

2. Can you explain what we know about the heterogeneity of ALS patients, and how different patients may respond to different treatments?

Response: Clinically, ALS varies in the site of onset (limbs vs speech or swallowing problems), relative amount of involvement of motor neurons in the brain vs the spinal cord, age at onset, and rate of disease progression. About 20 percent of people with ALS also have frontotemporal degeneration (FTD), which results in changes in behavior, personality, and language abilities due to loss of nerve cells in the frontal and temporal lobes of the brain. Genetically, dozens of genes are known to contribute to the disease, either by directly causing ALS or by increasing susceptibility to developing ALS. Gene

[1] pdbp.ninds.nih.gov/
[2] ninds.nih.gov/Current-Research/Focus-Tools-Topics/Biomarkers
[3] neurobiobank.nih.gov/
[4] markvcid.partners.org/about/consortium-overview

therapies tailored to specific causative mutations that cause about 17 percent of ALS cases are leading to the development of the most promising ALS treatments. An attractive strategy is to first characterize the pathologic processes in the genetically determined subset and then test if they are active in the more common sporadic cases. More research is needed to understand the causes of ALS in the sporadic, non-genetic, cases on a molecular and cellular level and to understand how those changes correspond to clinical heterogeneity so that we can better predict which people with ALS are most likely to respond to a particular treatment.

3. Can you describe the scientific research value in conducting open label studies, and their limitations?

   Response: The gold standard for assessing the safety and effectiveness of therapeutic interventions is a placebo-controlled, double-blind trial, in which neither the participant nor investigator have knowledge of treatment assignment to active or placebo. This type of study allows researchers to objectively compare clinical outcomes and adverse events between research participants who receive the investigational intervention and those who do not. In contrast, in open label studies, participants and the investigator or clinician administering a treatment know what treatment is given. Although open label studies can generate research data, there are limitations to the quality and value of these data. Both the knowledge of the intervention being administered, and the absence of a control group affect the usefulness of research data from open label studies. With knowledge of the treatment given, results regarding the efficacy of a treatment tend to be biased by beliefs or expectations the clinician or study participants have about the treatment. Moreover, the absence of a blinded control group makes it almost impossible in most cases to determine what changes in a patient's symptoms or disease progression are due to the investigational therapy, a placebo effect, or natural variability in a given disease. Biomarkers (biologic measures for monitoring disease progression, tracking treatment responses, or selecting patient populations) facilitate therapy development and successful clinical trials. Data from open label studies may contribute to the development of biomarkers and clinical outcome measures, but again, without blinding and a control group, it may be difficult to know whether and how the investigational therapy affects the measures being studied. Similarly, data from open label studies may complement natural history studies to understand disease progression, but any beneficial or adverse effects of the investigational therapy can confound the results. Beyond these biases and confounds, the availability of open label studies could affect recruitment for the more rigorous and translatable, blinded clinical studies planned or ongoing for the same condition, possibly slowing the development of other promising therapies.

The Honorable G. K. Butterfield (D-NC)

1. Emerging science on DNA repeat expansions, which is a focus of today's hearing, causes over 50 distinct diseases, including ALS, Huntington's disease, and another rare but devastating genetic disease, myotonic dystrophy. Myotonic dystrophy is a multi-

systemic inherited disease that affects at least 1 in 2,100 people or over 150,000 individuals in the U.S. Individuals affected by myotonic dystrophy can have skeletal muscle problems, heart function abnormalities, breathing difficulties, cataracts, issues with speech and swallowing (dysarthria and dysphagia), cognitive impairment, excessive daytime sleepiness, or diabetic symptoms.

Do you see an opportunity for a more focused NIH research program to investigate these multiple neurodegenerative conditions that includes additional funding to better understand the causes and accelerate treatments and eventually cures?

Response: The National Institute of Neurological Disorders and Stroke (NINDS) supports a broad research portfolio to determine the normal function of genes associated with neuromuscular and neurodegenerative diseases and how repeat expansions in those genes cause disease, to search for novel repeat expansions in people with unsolved difficulty with muscle control or coordination of voluntary movements and Huntington's-like disease, to develop generalizable methods for studying repeat expansions, and to identify potential therapeutic strategies that could be used for a number of diseases. For example, NINDS funds a project to identify a potential gene-based therapeutic strategy for myotonic dystrophy 1, which may also be applicable for developing treatments for other genetic diseases. Another NINDS-funded research study is conducting preclinical studies to determine whether a drug approved by the U.S. Food and Drug Administration (FDA) to treat infections has the potential to ameliorate sleep abnormalities in myotonic dystrophy. An NINDS-funded small business grant is identifying small molecules that have the potential to be further developed into drugs to treat myotonic dystrophy 1. Another small business funded by NINDS, Asuragen, has developed and commercialized a testing kit that rapidly and accurately detects and sizes DNA repeat expansions for myotonic dystrophy. More research funding for neurological and neuromuscular diseases would allow us to fund even more high-quality research and development projects to understand and develop new therapies for these devastating diseases.

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,[5] 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[6]

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

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 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. These include projects to 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 and others.

ARPA-H will provide an opportunity to build upon many principles the 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 could lead to new circuit treatments for neurological and psychiatric disorders.

ARPA-H projects will emphasize cross-cutting technologies with wide applications across diseases, including neurodegenerative diseases like Amyotrophic Lateral Sclerosis (ALS), to maximize the impact on patient outcomes. While ARPA-H will have a distinct culture as an independent agency within the National Institutes of Health (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.

Having witnessed the accomplishments of the first 7 years of the BRAIN Initiative, the field of neuroscience is enthusiastic about the value of this kind of transformational approach for neurodegenerative diseases.

3. 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: Alzheimer's disease and Alzheimer's disease related dementias (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.

The National Institute on Aging (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.

4. 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 Alzheimer's & Dementia Outreach, Recruitment & Engagement (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 AD/ADRD. 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 U.S. 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.

5. Some early research has associated SARS, MERS & 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[7], which aims to rapidly improve understanding of why some individuals who have symptomatic COVID-19 do not 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)[8] 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[9] run by the National Center for Advancing Translational Sciences (NCATS) 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,[10] 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.

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

6. 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 White individuals, 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 FOAs are suited for such research, and previous and currently active NIH grants fund similar follow-up studies on other ALS gene discoveries

7. 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,[11] 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 fiscal year 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.

8. 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 factors may be contributing to their improved survival?

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

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 Hawking 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.

9. Acting Commissioner, Dr. 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.

10. 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)

1. Dr. Koroshetz, being an expert in this area, would you agree that most of the early-stage research done regarding neurodegenerative diseases can't be done in humans because of ethics issues? Can you confirm that non-human primates at the National Primate Research Centers are the best models for this research? Why are non-human primates the best models to use for this research? 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 human brain is undoubtedly the most complex system in the human body, giving rise to our most uniquely human thoughts, behaviors, and actions. No system can fully replicate this complexity and researchers need an arsenal of tools to complete the picture. Of note, the National Institutes of Health (NIH) Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative studies have revealed that compared to the cerebral cortex of the mouse, the human cortex is over 1,000 times larger by area and the number of neurons. More recently, the BRAIN Initiative published details of the differences in brain cells comparing mouse with nonhuman primate and human brain cells. These studies suggest that first stage studies are best performed in rodents, but nonhuman primate models are often essential before moving experimental treatments to the human, as recently demonstrated by the development of the COVID-19 vaccine. Largely due to the similarity in brain structure, size and function, nonhuman primate models remain one of our best resources for understanding how the human brain functions in health and disease.

There is also concern that rodents, the primary animal model in neurodegenerative disease research, are much less vulnerable to neurodegeneration than humans. In contrast, some data from genetic studies suggest that nonhuman primates share a similar vulnerability for neurodegeneration as humans do. The immune response in rodents can differ greatly from the human. Furthermore, a major challenge in the treatment of adult neurological disorders is ensuring access of drug or biologic to the entire human brain. The human brain is 15 times larger than the mouse brain, thus nonhuman primates are a better model to assess the brain penetration of new therapies.

Nonhuman primate models are commonly used to explore the processing of complex information in the visual systems motor and auditory systems or cognitive function, and brain connectivity that exceed the capabilities of rodents. While advances in stem cell, organoid, and transgenic mice, as well as computational biology, non-invasive imaging, and other technologies are assisting our understanding of these systems, research on nonhuman primate continues to be essential because the relevant biology and behavior are simply not present or are too different from the human brain.

There are many examples of successful therapies that relied at some stage upon nonhuman primate studies, from the historic example of polio vaccine, to modern breakthroughs, including deep brain stimulation (DBS) for Parkinson's disease and gene targeted therapies for neurogenetic disorders. Because of their larger size and similar neural architecture to the human, nonhuman primates are also often the best model in which to test drugs in late stage preclinical development to ensure they meet milestones for safety and efficacy before exposing humans to experimental treatments.

NIH emphasizes the fact that animals in research are valuable resources that require appropriate care for and use of throughout the lifespan of research. Moreover, given the importance of the brain and the uniqueness of nonhuman primates, NIH recognizes that

this research may require special ethical considerations, and NIH continues to be a leader in this area. Ethical frameworks are woven throughout pioneering programs, like the NIH BRAIN Initiative, to ensure ethical stewardship over these essential research resources.

The Honorable Michael C. Burgess, M.D. (R-TX)

1. The 21st Century Cures Act was signed into law in 2016, promising America that Congress is committed to progressing innovative research that leads to new treatments for incurable diseases. One of the many important provisions in Cures was the establishment of the National Neurological Conditions Surveillance System at CDC. How do efforts of the National Neurological Conditions Surveillance System help researchers at the NIH understand and study neurologic diseases?

   Response: For many neurological diseases, we have incomplete information about how many people have these diseases and who those people are. The National Neurological Conditions Surveillance System will help better estimate prevalence, mortality, and incidence of neurological conditions; catalyze research into causes and prevention of neurological conditions; identify gaps in care and opportunities for basic science research; and increase public awareness to help better support impacted patients and their families. We are especially interested in the U.S. Center for Disease Control and Prevention (CDC) data that explore racial/ethnic, or socioeconomic disparities that affect the morbidity and mortality of neurological disorders so that we may fashion research to promote health equity.

   a. Can you explain any other efforts between the NIH and other agencies to collaborate on advancing research for these diseases?

      Response: The National Institute of Neurological Disorders and Stroke (NINDS) collaborates with agencies across the government to study neurologic diseases. The National Institutes of Health (NIH)Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative, which is developing a more complete arsenal of tools and information to revolutionize our understanding of how the brain functions both in health and disease, includes partnerships with the U.S. Food and Drug Administration (FDA), National Science Foundation (NSF), Defense Advanced Research Projects Agency (DARPA) and the Intelligence Advanced Research Projects Activity (IARPA), as well as numerous partners in the private sector. NINDS participates on a number of interagency coordinating committees and advisory groups that span the federal government. For example, the Interagency Pain Research Coordinating Committee, which is managed by NINDS, includes six federal Departments and agencies, and the Federal Research Subgroup of the Advisory Council on Alzheimer's Research, Care and Services includes many Departments, agencies, and offices across the government. Additionally, Department of Defense (DoD) and Department of Veteran's Affairs (VA) staff serve as ex officio members of the NINDS Advisory Council.

The Honorable Dan Crenshaw (R-TX)

As the COVID-19 pandemic has made clear, funding and commitment to clinical trials for innovative therapies can and will save lives.

The vast majority of the more than 850 active clinical studies in the U.S. (as well as those in Texas, where 27% of all U.S. studies are being conducted) are early stage (Phase 1 or Phase 2) studies that are led by academic research institutions or small biotechnology companies. This includes Texas-based organizations such as the Baylor College of Medicine, the Methodist Hospital System, M.D. Anderson Cancer Center, and the University of Texas Health Science Center, who are exploring the use of regenerative and cell-based therapies for conditions such as cancer, neurological conditions such as ALS and Parkinson's Disease, traumatic brain injury, spinal cord injury, osteoarthritis, and depression.

However, while NIH and other granting entities provide some funding for early-stage clinical trials, it's fairly minimal. In fact, both nationally and in my state of Texas, the NIH and other federal agencies provide a limited amount of support to only about 19% of all active clinical trials. This is particularly problematic for academic research institutions and small biotechs, who are responsible for the majority of trials. As a result, many studies end up never getting to patients.

Dr. Mya Schiess at the University of Texas Health Science Center is the Principal Investigator for a Phase 2a study studying the use of allogeneic bone marrow-derived mesenchymal stem cell infusions to slow the progression of Parkinson's disease. This study is funded primarily by philanthropy.

1. Studies like this could die on the vine if we don't support late-stage clinical trials, can you commit to working with me to move the NIH to support clinical trials—particularly later stage trials—so that we actually get the therapies into the hands of patients?

   Response: The National Institutes of Health (NIH) plays an important role in supporting clinical research and clinical trials, including early and late-stage trials. In fiscal year 2020, NIH spent over $6 billion overall on clinical trials and supportive activities and about $1 billion on late stage phase 3 trials. NIH funding for clinical trials complements support from the private sector by funding trials that may not receive industry support, such as trials focusing on rare diseases with small commercial markets, comparing the effectiveness of different available drugs, exploring new uses for previously developed therapies, or assessing interventions that address public health needs with limited potential for profit. Clinical trials are expensive, and they also have a high failure rate, which presents significant risk for funders. NIH support for preclinical and clinical research helps to de-risk potential new treatments to a point where they are more likely to attract private sector investment and to prepare for successful clinical trials through natural history studies and the development of biomarkers and clinical outcome measures. In addition, NIH support for early-stage clinical trials helps provide clear

evidence for whether continued investment in later stage development is warranted, either through NIH programs or external sources. The National Institute of Neurological Disorders and Stroke (NINDS) has targeted funding opportunities for early and late stage clinical trials, and to increase the efficiency and quality of clinical trials for neurological disorders, NINDS supports four clinical trials networks: the NIH StrokeNet supports trials in stroke prevention, acute treatment, and recovery; NeuroNEXT supports phase 2 clinical trials and biomarker studies for neurological disorders other than stroke; SIREN, jointly funded with the National Heart Lung and Blood Institute (NHLBI) supports trials for emergency care interventions, and EPPIC-Net, led by NINDS for the HEAL Initiative[SM], supports studies on pain interventions. These networks and others supported across NIH provide accessible infrastructure for early and late-stage clinical trials, bring together communities of experts to promote high-quality research, enable partnerships with industry and patient organizations, and help train future clinical trial investigators.