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Subcommittee on Health
The Path Forward: Advancing Treatments and Cures for Neurodegenerative Diseases
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Introduction

Chairman Pallone, Ranking Member McMorris Rodgers, Chair Eshoo, Ranking Member Guthrie, and Members of the Committee – thank you for the opportunity to submit testimony.

I am Dr. Matthew Rizzo – a physician, a researcher, a neurologist, and a professor. I am also a husband, son, father, and friend. I sincerely appreciate the opportunity to submit this testimony on an issue of great professional interest and great personal importance to me and so many other Americans.

I currently serve as the Frances & Edgar Reynolds Chair & Professor of the Department of Neurological Sciences, Director of Neurosciences Services, and Co-Director of the Center for Integrative and Translational Neuroscience at the University of Nebraska Medical Center, as well as Director of the NIH/NIGMS Great Plains IDeA Clinical and Translational Research network. I received my medical training at Johns Hopkins University School of Medicine in Baltimore, MD and completed my residency in Neurology and fellowship in Behavioral Neurology and Cognitive Neuroscience at the University of Iowa in Iowa City. Prior to joining the University of Nebraska Medical Center, I served as a Professor of Neurology at the University of Iowa College of Medicine; Vice Chair of Transitional and Clinical Research, Department of Neurology at the University of Iowa College of Medicine, and as the Director of the Aging Brain and Mind Initiative at the University of Iowa. They do research and provide care for patients with memory disorders, particularly focusing on addressing behavioral consequences of aging and neurological disorders.

The American Brain Coalition

I am also honored to serve as the Chair of the American Brain Coalition (ABC). The ABC is a nonprofit organization comprised of over 125 of the nation's leading professional neurological, psychological, and psychiatric associations and patient organizations. Together, the ABC seeks to advance the understanding the brain and reduce the burden of brain disorders for the millions of Americans who suffer from diseases affecting the brain and central nervous system.

The Staggering Toll of Neurodegenerative Disease

The ABC and I are grateful for the Committee's attention today to neurological disorders and the burden these disorders have on patients and their families. Brain diseases, including neurological, psychiatric, and central nervous system disorders, impose staggering personal and financial costs on Americans.

Nearly one in five U.S. adults live with a mental illness. Neuropsychiatric disorders are also the leading cause of disability in the nation, making up 18.7% of years lost to disability and premature death.[1] Neurological conditions are troublingly prevalent as well - twenty million Americans suffer from a

[1] Office of Disease Prevention and Health Promotion, Mental Health and Mental Disorders, at: https://www.healthypeople.gov/2020/topics-objectives/topic/mental-health-and-mental-disorders.

neurological condition, with 16% of households including an individual with a brain impairment.[2] Brain and CNS diseases also harm older Americans, with more than one in nine people over age 65 having Alzheimer's dementia.[3]

The enormous personal costs of brain and CNS conditions also translate to financial hardship for patients and their families, and burden the U.S. economy. Brain disorders and diseases cost the U.S. more than $1.5 trillion per year,[4] a significant portion of which is borne by the Medicare program. Seven of the twenty-one chronic conditions tracked by the Centers for Medicare and Medicaid Services are related to the brain, representing an average annual cost of $23,325 per Medicare beneficiary – higher than the average cost for all other chronic conditions.[5]

The high prevalence of these diseases means that nearly every family in the United States has either personally experienced a brain disease or watched a loved one struggle with the effects of diseases like substance use disorder, schizophrenia, multiple sclerosis, Alzheimer's disease, and hundreds of other diseases that impact the brain.

Unique Translational Hurdles for Neurodegenerative and Other Brain-Related Diseases

Despite the prevalence and impact of these diseases, few effective treatments are available for many brain diseases and disorders. While product development is difficult for any condition, treatment development for brain disease is uniquely challenging. In particular:

- Clinical trials for brain and CNS conditions fail more often and are frequently more costly than clinical trials for other conditions.[6]
- Brain-targeting drugs, devices, and other therapeutics reviewed by the Food and Drug Administration (FDA) are also approved at a much lower rate than those for other disease areas, with one recent study finding that the mean approval phase time for CNS compared to non-CNS was an astonishing 57% longer.[7]
- A recent report indicated that the probability of a drug successfully making its way through a Phase 1 clinical trial to the point of approval is only 15% for brain and CNS treatments — compared to 32% for ophthalmology, 25% for cardiovascular problems, and 25% for infectious disease.[8]

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[2] S. Pal, Incidence and Prevalence of Major Neurologic Disorders. US Pharm, at: https://www.uspharmacist.com/article/incidence-and-prevalence-of-major-neurologic-disorders

[3] Alzheimer's Association, Facts and Figures, at: https://www.alz.org/alzheimers-dementia/facts-figures.

[4] Information Technology & Innovation Foundation, A Trillion-Dollar Opportunity: How Brain Research Can Drive Health and Prosperity, at: http://www2.itif.org/2016-trillion-dollar-opportunity.pdf?_ga=2.209915987.77733799.1607703298-1777725734.1607703298.

[5] Center for Medicare & Medicaid Services Chronic Conditions Utilization/Spending State Level: All Beneficiaries 2017. The average per capita spending for a chronic condition is $22,099.

[6] J.A. Dimasi, CNS drugs take 20% longer to develop and to approve vs. non-CNS drugs. Tufts Center for the Study of Drug Development.

[7] See Bio, Clinical Development Success Rates and Contributing Factors 2011-2020, at: https://www.bio.org/clinical-development-success-rates-and-contributing-factors-2011-2020; J.A. Dimasi, CNS drugs take 20% longer to develop and to approve vs. non-CNS drugs. Tufts Center for the Study of Drug Development.

[8] C. Heem Wong, et al. Estimation of clinical trial success rates and related parameters. Biostatistics, kxx069.

These delays compound the fact that not enough treatments exist – every extra expense and every delay means more time that our families, friends, and neighbors suffer from the frequently debilitating effects of these diseases.

Treatments Lag Behind Neuroscience Breakthroughs

The lack of safe and effective treatments for brain disease is particularly frustrating given the incredible neuroscience discoveries made in the past decade. In addition to private investment, robust public investment in the National Institutes of Health (NIH) and the creation and funding of the BRAIN Initiative, we are building the knowledge base that will allow us to finally deliver treatments to patients that need them.

In Nebraska, we recognize that these are critical times for advancing patient care, education, research, and community outreach for mind and brain health. Physicians, researchers, educators, students, and all our colleagues have responded with aplomb, resilience, and innovative solutions. Our goal is to support brain health and the treatment of neurological disorders and diseases across the lifespan. People have long dreamed of living forever with a "youthful" brain. Unfortunately, time generates wear and tear on the brain. Along with genetic and environmental stress and trauma (including socioeconomic factors and ongoing COVID-19 pandemic), this eventually leads to failure at cellular and network levels, cognitive aging, and brain diseases, which limit the computing power of the motor and neurosensory systems.

Ambitious engineers hope to extract human consciousness and put it in artificial processors able to hold the experience and unique processing capacity that form our individuality. The sheer number of neurons (over 80 billion), connections between single neurons (up to 10,000), total number of interconnected neurons, and ignorance of relevant systems science and minimal requirements to generate any kind of consciousness put this dream out of reach so far. Others hope to understand the restorative capacity of the brain and replace and integrate elements as they die or to delay the demise of neurons so that they last as long as our bodies last. These approaches include attempts to delay mental decline before it becomes clinically significant through increased mental and physical activity and caloric restriction.

For example, ongoing work aims to discern and delay different phases of Alzheimer's disease (AD) progression and correlate these phases with declines in vasculature, lipid metabolism, and neurotransmitters. Phases of decline preceding cell death are biochemical, cellular, and clinical. Of note, the biochemical phase begins decades before the cellular phase, which in turn begins years before the clinical diagnosis of AD. AD does not simply "happen" at a late stage of life, but builds up slowly long before it becomes clinically relevant. Understanding these early phases of a devastating disease that affects many older Americans is clearly important. Early diagnosis could allow early treatment to counteract early progression over many years and delay dramatically the clinical phase in AD and related disorders where preclinical phases antedate diagnosis by decades.

Healthcare Comes Home and the Brain in the "Wild"

Our research teams at Nebraska use clinical trials, imaging, human factors/ergonomics, human systems integration, simulation, and novel tools to synchronize sensor signals and glean digital biomarkers from continuous decades of big, real-world data from a person's own environment—at home, at work, at play, and in transit— to answer fundamental questions translatable to clinical research and practice. At a systems level we are pioneering egalitarian platforms for personalized care, with attention to the underserved and forgotten, and with a focus on diversity, equity and inclusion. Our research, supported by the NIH and industry, underscores bidirectional links between real-world behavior in health and

disease, along with the most promising evidence-based measures and effective configurations of sensor technologies for recovering health-relevant data from behavior. We have even extended this data collection to automobile driving, in line with the NIH "All of Us" efforts to collect prospective data from up to a million people in the field. In this work, a person's own car and ubiquitous personal sensors capture a wide variety of health data, paving the way for egalitarian access to healthcare diagnostics outside the traditional confines of a hospital or clinic. These results are then confidentially shared with medical practitioners and researchers through the electronic medical record to address impactful conditions such as AD, and associated neurodegenerative disorders like Parkinson's Disease, Huntington's Disease, Lewy Body Disease, ALS, and many others that affect cognition and processing speed. This also addresses a range of common medical conditions affecting perception, attention, sleep, mobility, and mood. In addition, this technology can be applied to the emerging need to track post-acute sequelae of the SARS-CoV-2 infection in the aftermath of the current COVID-19 pandemic. These same approaches can be used to track the efficacy of drugs, biological agents and devices in the real world, a critical need expressed by the NIH and FDA. Innovative research like this demonstrates the promise of public and private investment in neuroscience research – and the need for federal regulators to be prepared to address unique technologies and treatment modalities as neuroscience continues to advance.

Building Bench to Bedside Pipelines for Brain Health

Basic research remains fundamental to scientific advancement and underpins translation of research from "bench to bedside," a pinnacle achievement of enlightened society and government. Sometimes called "bench" or T0 research, basic research remains central to understanding mechanisms and models and informing theories of human aging and disease. It includes a range of preclinical approaches, including animal models of aging and disease, in vitro studies, computational models, technological tools, and others, to discover new pathways, pathophysiology, or treatments. Relevant to mind and brain health, the NIH seeks to link medical science discovery with community and societal needs through strategic clinical and translational science (CTS) strategies that apply basic laboratory and preclinical discoveries to develop trials and studies in humans and advance best practices for community adoption. The NIH CTS Awards (CTSA) created dozens of academic sites to build clinical and translational research (CTR) capacity at local, regional, and national levels. Similarly, CTR programs build CTR infrastructure across states traditionally receiving less NIH support. These and other federal programs, together with industry and patient advocacy groups like the American Brain Coalition, help span silos to advance mind and brain health across the lifespan. Similar innovative, silo-spanning efforts are also needed at the FDA to further discoveries and advance the translational science and clinical trials spanning multiple modalities and combined approaches to treatments and cures.

The Case for a Neuroscience Center of Excellence

In order to respond to the unique challenges in the discovery and development of treatments for brain disease, and allow more neuroscience discoveries to directly benefit patients, it is vital that federal government prepare the brain-specific regulatory tools and guidelines needed for fast, well-structured, transparent, and predictable product review. To support this aim, ABC and the brain community are advocating for Congress to create a Neuroscience Center of Excellence at the FDA. Such a center will foster innovation in the regulation and development of treatments for brain diseases and disorders. We are pleased to see this goal supported in the recent bipartisan 'Cures 2.0' discussion draft offered by Representatives DeGette and Upton. We look forward to being a resource to them and to the Committee as that legislation moves through the process.

While there are understandable differences between oncology and neuroscience, the Oncology Center of Excellence at the FDA created through the 21st Century Cures Act is a useful model to demonstrate how a Center of Excellence can speed access to safe and effective treatments and meaningfully engage the patient community in the development and regulation of drugs, devices, and biologics. The successes of the Oncology Center of Excellence demonstrate that, with resources and a singular focus, the FDA can provide the guidance and programs necessary to speed safe and effective treatments to market.

Like cancer, there are unique regulatory considerations for drugs, biologics, and devices that target the brain, and these call for a unique and targeted regulatory approach. By creating a Neuroscience Center of Excellence with resources dedicated to meet this challenge, FDA can create a fair and transparent process that breaks down internal silos and allows developers to seek FDA guidance and eventually bring safe and effective brain-targeting treatments to market. These tools will ensure a level playing field for treatment development and give patients the opportunity to inform the development and regulation of these products, while having the confidence that FDA-approved products are safe and efficacious.

A problem like brain disease requires a focused, urgent response that takes seriously the incredible burden borne by patients who often face poor prognoses and have access to too few treatments. Every day that a safe and effective treatment for a brain disease or disorder is delayed unnecessarily is another day where millions of patients suffer from potentially debilitating disease. ABC urges the Committee to establish a Neuroscience Center of Excellence. With this center, FDA will be able to create more transparency and predictability in the development and regulation of brain treatments and smooth the translational path for brain disease treatments and cures.

Thank you for the opportunity to provide this testimony. The American Brain Coalition looks forward to continuing this dialogue and identifying creative policy solutions to bring more treatments and cures to patients with neurological and psychiatric disease.