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The Path Forward: Advancing Treatments and Cures for Neurodegenerative Diseases

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Good morning, Chair Eshoo, Ranking Member Guthrie, and distinguished members of the Committee. We are Richard J. Hodes, M.D., Director of the National Institute on Aging (NIA), and Walter J. Koroshetz, M.D., Director of the National Institute of Neurological Disorders and Stroke (NINDS), two of the 27 Institutes and Centers of the National Institutes of Health (NIH). It is an honor to be here today to update you on our progress addressing a public health issue of considerable urgency: the need for effective treatments and compassionate care for persons living with neurodegenerative disorders and their care partners. We look forward to telling you about some of the many ongoing initiatives and important advances in research targeting the development of treatments and prevention strategies for these diseases, including Alzheimer's and related dementias (AD/ADRD) and amyotrophic lateral sclerosis (ALS), supported by the appropriations provided by Congress in recent years.

BURDEN OF NEURODEGENERATIVE DISEASES

Neurodegenerative disorders result from progressive damage to cells and nervous system connections that are essential for functions including cognition, mobility, coordination, strength, and sensation. Millions of Americans are affected by neurodegenerative disorders each year, exacting an incalculable personal toll and a tremendous economic cost in medical expenses and lost productivity. According to a recent estimate from the Centers for Disease Control and Prevention (CDC), Alzheimer's and Parkinson's disease are the sixth and 14th leading causes of death in the United States, respectively.

Neurodegenerative diseases are among the most common late-life diseases, and the number of Americans with these diseases is expected to increase as the population ages. According to a recent NIH-funded analysis, an estimated 6.25 million Americans are now living with Alzheimer's dementia, a progressive brain disease that slowly destroys memory and thinking skills and eventually even the ability to carry out the simplest tasks of daily living. A majority of those affected are women. By 2050, the estimate increases to about 12.7 million Americans with Alzheimer's and to more than 13.8 million in 2060. These estimates undoubtedly include many Americans with Alzheimer's-related dementias, such as Lewy body dementia (LBD), frontotemporal dementia (FTD), vascular contributions to cognitive impairment & dementia (VCID), and mixed dementias. These dementias share clinical and pathological features with Alzheimer's. In fact, most dementia cases exhibit a mix of pathologies. In addition, another 500,000 to 1.5 million Americans have Parkinson's, a degenerative movement disorder.

Neurodegenerative disorders also include rare but devastating conditions like ALS, a rapidly progressive, fatal disease that affects the nerve cells controlling voluntary movement. The CDC estimates that 12,000–15,000 Americans have ALS, and approximately 5,000 Americans are newly diagnosed with ALS each year. ALS is classified as a rare disease because it affects fewer than 200,000 Americans at any time. The disease is rapidly fatal, with a median survival time of 20 to 48 months.

Some of those affected have more than one neurodegenerative disease. Post-mortem studies show that most older adults diagnosed with Alzheimer's also have pathology in brain blood vessels with consequent small strokes and thinning of the brain's connecting wires ("white matter disease"). Many also have accumulations of proteins that are a hallmark of LBD or FTD. At least 75 percent of people with Parkinson's who survive for more than 10 years will develop dementia. Because ALS and FTD frequently co-occur, most researchers now believe ALS and some forms of FTD are related disorders and call them ALS-FTD spectrum disorders.

The burden of dementia is rising among racial and ethnic minority groups. Alzheimer's disease risk in African Americans is nearly twice that of non-Hispanic whites. Certain factors, including socioeconomic status and higher prevalence of cardiovascular issues, put some Hispanic/Latino Americans at increased risk for developing dementia. As a result, the number of Black/African Americans with Alzheimer's is expected to increase from about 1.1 million currently to 3.1 million people by 2060. During that same time frame, the number of Hispanic/Latino Americans with Alzheimer's is expected to increase from about 0.76 million to 3.7 million people.

Recent increased funding for neuroscience research and research into neurodegenerative disorders, including funding for Alzheimer's and related dementias and the BRAIN Initiative, has enabled NIH to make key advancements in the understanding of neurodegenerative diseases and identify promising new avenues for prevention and treatment. However, effective treatments that can cure or slow the progressive death of nerve cells in the neurodegenerative disorders remain elusive. To break through this treatment barrier, NIH supports research across the therapeutic development pipeline, from basic science to better understand these conditions and identify promising targets, to clinical trials of potentially disease-modifying interventions to prevent and treat these disorders. In doing so, NIH uses a cross-cutting approach that emphasizes broad engagement with the research community as well as with those living with these conditions to work toward the development of successful interventions, tools, and support for people living with neurodegenerative disorders and for their families and other care partners.

CORE PRINCIPLES FOR NEURODEGENERATIVE DISORDER RESEARCH AND THERAPY DEVELOPMENT

NIH research efforts across the therapeutic development pipeline for neurodegenerative disorders reflect several core principles that enhance the research enterprise and are essential for progress against neurodegenerative disorders.

Diversity, inclusion, and promoting health equity

NIH has a long history of investments to better understand and reduce or eliminate health disparities for many conditions and diseases, including by:

- Providing researchers with resources and opportunities to ensure their studies represent the diverse racial and ethnic composition of the U.S. population, including those most at risk for developing particular neurodegenerative disorders,
- Advancing health equity and health disparities research through new funding opportunities to explore why there are differences in neurodegenerative disorder incidence and care among diverse populations, and
- Enhancing the diversity of the research workforce through NIH-funded training programs

To ensure that prevention and treatment interventions will be effective for all people with these disorders, investigators must enhance and expand recruitment of research participants from diverse populations.

Open Science and Data Sharing to Promote Collaboration

Sharing scientific data helps validate research results, enables researchers to combine data types to strengthen analyses, facilitates reuse of hard-to-generate data or data from limited sources, and accelerates ideas for future research inquiries. NIH's investments in centralized data-sharing platforms and other technologies make it possible for scientists to share data, biological samples, methods, and other crucial research resources more broadly and effectively. The resulting large sets of data—often

referred to as "big data"— provide the basis for discoveries that are revealing new molecular mechanisms of neurodegenerative disorders, providing more pathways to potential therapeutic targets and biomarkers.

Open science and data sharing initiatives such as the Accelerating Medicines Partnership programs for Alzheimer's and Parkinson's, the Parkinson's Disease Biomarkers Program, the Clinical Research in ALS and Related Disorders for Therapeutic Development Consortium, and similar NIH initiatives have fostered a team science environment. These programs have transformed the way that scientists collaborate rather than compete, share their data and biological samples, work together to discover new biological mechanisms of disease, and find new drug candidates for testing.

Rigor and transparency

Rigor—the overall quality of the experimental process—is the essence of scientific research. NIH has several efforts underway to enhance rigor and reproducibility in scientific research. For example, NINDS is developing a framework for advancing rigorous research that will include the formation of an educational platform on relevant principles as well as the establishment of networks of rigor champions in the research community. In recent years, NIA has partnered with the NIH Library, the Alzheimer's Drug Discovery Foundation, and the Alzheimer's Association to create the Alzheimer's Disease Preclinical Efficacy Database (AlzPED). This database uses a "rigor report card" listing a standardized set of study design elements to monitor the rigor of studies and serve as a roadmap to increased rigor.

Community engagement at all levels of the scientific process

NIH engages people living with neurodegenerative conditions and their families in setting priorities, planning, and conducting research. The priorities of individuals living with neurodegenerative conditions and their families may not always be apparent to those not experiencing the problems that a disease presents. For example, individuals with Parkinson's disease have stressed the importance of non-motor symptoms on their quality of life. Patient advocacy organizations also provide insight that can greatly improve the efficiency and effectiveness of research, not only in recruiting for clinical studies, but also in many other aspects of studies involving human participants, including reducing barriers to participation. NIH utilizes several mechanisms to engage persons living with neurodegenerative conditions and other stakeholders, including annual meetings such as the NINDS Nonprofit Forum and annual research summits on Alzheimer's, AD-related dementias, and caregiving.

UNDERSTANDING NEURODEGENERATIVE DISEASES

The biggest obstacle to developing interventions to prevent or treat neurodegenerative disorders is our incomplete understanding of the complex causes of each neurological disorder and its subtypes, of what drives progression, and of the factors that could be modulated for recovery of function. Understanding the underlying biology of neurodegenerative diseases at multiple levels using model organisms, tissue and cell platforms, and human subjects research is essential for developing rational strategies to treat these diseases.

Genes, proteins, and other molecules

Studies of genes, proteins, and other molecules have revealed that many neurodegenerative diseases share common molecular and cellular mechanisms and processes. Therapies that target these processes rather than disease-specific proteins may be broadly beneficial for addressing multiple neurodegenerative diseases.

Progress in our understanding of the genetics of familial forms of neurodegenerative diseases gives us insights into the mechanisms underlying more common spontaneous (non-inherited) forms of these disease. For example, almost 25 years ago NIH intramural investigators studying a large family with a history of Parkinson's disease identified a mutation in the alpha-synuclein gene as the first known genetic mutation associated with Parkinson's disease. Although this gene mutation is rare, the finding led to the discovery that alpha-synuclein protein aggregation inside neurons is the pathological hallmark of LBD and almost all forms of Parkinson's disease. The led to numerous research studies investigating how alpha-synuclein functions at a cellular level, developing biomarkers for detecting alpha-synuclein in persons to aid in early diagnosis or monitor disease progression, and developing new treatments that target alpha-synuclein accumulation.

Similarly, genes first discovered in families that had inherited forms of Alzheimer's played a key role in advancing our understanding of the disease. Researchers have identified three different mutations which cause the production of harmful forms of amyloid plaques, a hallmark of Alzheimer's disease. These discoveries paved the way for several avenues of research: we now have multiple biomarkers to detect the presence of amyloid in the brain, and NIA-supported teams are working to develop less invasive and less expensive versions of amyloid tests. Moreover, several drugs are now in clinical trials that target amyloid to possibly treat or prevent Alzheimer's. Aducanumab was recently granted accelerated approval by the Food and Drug Administration (FDA). In explaining its decision, FDA noted that the drug's ability to reduce amyloid in the brain "is expected to lead to a reduction in the clinical decline" of Alzheimer's. Additional research is essential to test the ability of amyloid-targeted treatment to affect clinical outcomes.

After years of making progress understanding the role of single genes or proteins, we now have advanced technologies that make it possible to conduct large-scale analyses of multiple genes or proteins and integrate the information with clinical data to better understand disease and new therapeutic targets. Late last year, an international team led by scientists from NIA and NINDS discovered a connection between ALS-FTD and the genetic mutation that causes another neurodegenerative condition, Huntington's disease. This discovery was made possible via whole genome sequencing, in which investigators screen the entire set of genes of a large group of individuals. The discovery might translate into a new way of diagnosing and treating some individuals with ALS-FTD. In fact, clinical trials of gene therapy targeting the mutated gene are already in progress with those who have Huntington's. The investigational gene therapy may help people with ALS-FTD with this gene mutation.

NIH launched the Accelerating Leading-edge Science in ALS (ALS^2) initiative, part of the NIH Common Fund's Transformative Research Awards. This initiative aims to dramatically advance our understanding of what triggers ALS and what drives the rapid progression of this disease. ALS^2 employs a three-pronged strategy to accelerate ALS research focused on: 1) employing emerging technologies from neuroscience and other fields; 2) attracting new talent from diverse scientific disciplines; and 3) understanding disease convergence.

An area in which we have made remarkable progress is in the complex genetics of AD/ADRD. Initiatives such as the Alzheimer's Disease Sequencing Project, the Late-Onset Alzheimer's Disease Family Study, and many others continue to provide important insights into the causes of these diseases. For example, we now know from our studies of genetics in combination with clinical and pathological studies that Alzheimer's is not a single entity; rather, several different brain pathologies lead to a similar

set of symptoms that are clinically classified as Alzheimer's—underscoring the fact that a "one-size-fits-all" approach to treating the disease may not be appropriate and highlighting the need for personalized diagnosis and treatment.

The Accelerating Medicines Partnership (AMP) is a public-private partnership among NIH, FDA, biopharmaceutical and life science companies, and nonprofit organizations. The goal is to transform the current model for developing new diagnostics and treatments by jointly identifying and validating promising biological targets for therapeutics. The AMP for Alzheimer's Disease enabled research teams to identify and make publicly available more than 500 unique candidate drug targets. A second phase of the program, launched this year, will expand the characterization of Alzheimer's through the analysis of human brain samples and inform the development of therapies that can be tailored to an individual's unique disease risk profile. AMP for Parkinson's Disease is leveraging existing cohorts collected by NIH, the Michael J. Fox Foundation, and the Harvard Biomarker Consortium and biosamples resources to perform large-scale analyses of genes and their products (e.g., proteins) to identify and validate biomarkers and new therapeutic targets for Parkinson's as well as enable the development of therapies customized to an individual's unique disease profile.

The Brain and Its Cells

Individual neurons (brain cells) communicate with other neurons to form circuits and networks of millions of neurons with trillions of connections that perform all of the functions of the brain and spinal cord, such as processing sensory information, storing memories, and controlling movement. We know that the degeneration and dysfunction of neurons affects how those circuits process information and lead to loss of memory, inability to control movement, or other symptoms of neurodegenerative diseases. The NIH BRAIN Initiative accelerates the development and application of innovative technologies to develop tools that empower researchers to answer previously unapproachable questions about how individual cells and complex neural circuits interact. These tools are filling gaps in knowledge and provide unprecedented opportunities for exploring new ways to treat and prevent brain disorders, including neurodegenerative disorders.

The development of brain cell "atlases" —comprehensive resources describing the structure, composition, and interactions among brain cells—is an essential step toward understanding how the brain works and fails in disease. The Human Brain Cell Atlas project will generate comprehensive brain cell atlases in humans and other species. Built from the characterization of millions of individual brain cells, it will establish data infrastructure, analytics, and applications for brain cell types that are accessible to the neuroscience research community. Tools developed in the BRAIN Initiative are now being used to precisely define the cellular changes that occur in the various stages of neurodegenerative diseases as well as disturbances in the connections among cells.

The Armamentarium for Brain Cell Access will generate and implement methods to access, mark, manipulate, and model specific cell types across multiple species, including humans. The long-term goal is to provide precise access and manipulation tools for therapies targeting interconnected brain cells. The Armamentarium leverages information revealed by brain cell atlases to identify molecular targets for selectively accessing specific types of cells.

Interactions between Body Systems

We are increasingly learning that other body systems, such as the digestive and vascular systems, can give us important clues into the disease process and may even provide strategies for treating or preventing these diseases. Scientists have been exploring how the community of microbes in our

digestive tract—known as the gut microbiome—affects our health. Some of the substances released by the gut microbiome are beneficial to our body whereas others are harmful. Early research suggests that these substances can impact brain health. For example, a recent analysis of publicly available data from the NIA-funded Alzheimer's Knowledge Portal of more than 2,000 brain samples provided evidence that microbial waste products, which can travel through the bloodstream and enter the brain, may play a role in Alzheimer's.

Mounting evidence shows that the gut microbiome also plays a role in Parkinson's disease. Recent studies have shown that alpha-synuclein aggregates accumulate in the nerves that line the gut, even years before motor symptom onset, and there is also evidence suggesting that alpha-synuclein aggregates may travel from the gut to the brain via the vagal nerve and that the microbiome may affect the initial accumulation of alpha-synuclein aggregates in the nerves of the gut. While still preliminary, the role of the digestive system and gut microbiome in triggering the development of Parkinson's disease is an active area of research that may lead to new prevention or treatment strategies.

The cardio- and cerebrovascular systems can have a profound influence on cognition and dementia. To better understand why neurovascular damage occurs and how it contributes to cognitive decline, NIH supports a number of clinical consortia, such as DISCOVERY and Diverse VCID. In addition, basic research projects are trying to understand the relationship between brain cells and their blood vessels (the "neurovascular unit"). Typically, the blood-brain barrier functions to protect the brain from harmful substances while allowing in glucose and other needed substances. Breakdown of the blood-brain barrier may lead to inflammation of the brain, which may amplify or cause symptoms of dementia. This barrier poses a particular challenge in drug development: designing drugs that can cross the barrier to reach intended targets in the brain without causing leakage across the blood vessels, a side effect of some anti-amyloid therapies.

Model Systems

Genetic engineering has enabled scientists to model the mechanisms of key steps in disease by utilizing flies, mice, or other organisms with the mutations that cause human disorders, making them valuable tools for studying disease and testing new therapies. NIH supports research across the full spectrum of models, as appropriate to the scientific questions, with careful attention to ethical conduct of research and oversight frameworks, and funds programs aimed at developing and distributing new animal models. For example, research teams that are part of the NIA-supported Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease (MODEL-AD) consortium have created more than 50 genetically modified mouse models. These mice are available to the research community through The Jackson Laboratory, and the data, protocols, and other resources are available via the AD Knowledge Portal. In addition, the NINDS Development and Validation of Advanced Mammalian Models for FTD, LBD, VCID, and mixed dementias resulted in several new projects. These will help fill the critical need for next-generation animal models for many types of dementia.

For some types of studies, nonhuman primates are critical model organisms because of their anatomical, physiological, and behavioral similarity to humans. A potential cause of the multiple failures of translation from animal models to humans is an over reliance on rodent studies. Nonhuman primates' vulnerability to neurodegenerative disease is likely closest to that of humans, and the common marmoset has emerged as a promising model system for understanding the primate brain and associated disorders. The 13 NIH Institutes, Offices, and Centers in the NIH Blueprint for Neuroscience and the BRAIN Initiative support marmoset colonies, and the NINDS intramural program has established such a colony,

which will advance research on neurodegenerative disorders. NIH takes animal welfare seriously and has numerous policies and protocols in place to assure the ethical treatment and use of these invaluable resources. All NIH-funded research with animals is reviewed to ensure that (1) the science is highly meritorious, (2) the use of nonhuman primates is absolutely required, and (3) the welfare of the animals is protected.

NIH also supports the development and utilization of research approaches that may reduce the necessity for using animal models and improve the efficiency and effectiveness of research. Human induced pluripotent stem (iPS) cells, that is, stem cells originally derived from a person's skin or blood cells, contain a person's entire genetic code, which enables better understanding of how different gene and proteins interact, and can be used to create three dimensional structures, such as the "tissues-on-a-chip" system to model spinal cord tissue in ALS, that more accurately replicates the cellular environment than a petri dish. The NINDS Human Cell and Data Repository provides iPS cells from people with a wide variety of neurodegenerative diseases to the research community.

In early 2021, investigators at the new intramural Center for Alzheimer's and Related Dementias (CARD), a collaborative NIA/NINDS initiative that enhances research on Alzheimer's and related dementias, and their collaborators documented efforts to create "personalized" stem cells for studying dementia. This project is designed to engineer cell models of disease-causing gene mutations from multiple brain disorders, including Alzheimer's, ALS-FTD, and other dementias. The resulting library of cell lines, which will be freely available to the research community, can be used for disease modeling and drug development.

NIH is also developing an array of technologies, including advanced imaging techniques, that can noninvasively study the structure, function, and biochemistry of the human brain.

TRANSLATING DISCOVERIES INTO THERAPIES

NIH-supported research catalyzes progress across the public and private research ecosystem for neurodegenerative disorders in many ways. NIH supports proof-of-concept demonstrations and other endeavors that bridge the drug development transition from basic and translational research to early-stage clinical trials to de-risk innovative therapeutic development strategies and attract private sector investment. NIH also works to compress the timeline for developing treatments wherever possible, from developing robust biomarkers to sharing data and tools and streamlining recruitment for clinical trials.

As knowledge advances, scientists are developing more precise treatments and preventions aimed at specific neurodegenerative disorders. In addition to drugs aimed at a specific disease pathway, NIH-funded researchers also are exploring many variations of targets simultaneously, considering combinations of treatments, and working to repurpose existing drugs to treat these diseases.

As an example, NIA recently funded several new projects through its Alzheimer's Drug Development Program. Each project is focused on developing a new drug that targets a different biological process, such as brain inflammation, known to go awry during the development of Alzheimer's and related dementias. If successful, these NIH-supported preclinical drug development studies will result in new candidate drugs that could then be tested in people.

The Blueprint Neurotherapeutics Network, which is a collaboration of eight NIH Institutes and Centers, provides support for early-stage small molecule drug discovery through phase 1 clinical testing and has supported 30 projects over the last decade. Three compounds developed through Blueprint have entered Phase 2 clinical trials in patients, including one for Alzheimer's disease. Currently Blueprint is funding three projects on Alzheimer's disease and one for Parkinson's disease, and this successful program has been expanded to include biologics.

The NINDS Translational Research Program provides a suite of resources to academic and industry researchers to advance early-stage neurological technologies, devices, and therapeutic programs to industry adoption (i.e., investor funding and corporate partnerships). The program currently supports several projects on neurodegenerative diseases being conducted by academics and small businesses.

Gene-based therapies are emerging as promising therapeutic strategies for neurodegenerative diseases, both for people with identified genetic forms of the disease and for people with more common spontaneous forms. NIH continues to play a large role in funding preclinical studies for gene-based therapies that are now being pursued by industry. Findings from an NINDS-funded preclinical study became the foundation of an ongoing industry-funded Phase 3 clinical trial that is testing small, synthetic molecules (called ASOs) designed to target a specific gene (SOD1) in patients with SOD1-linked ALS. In 2017, NINDS-funded scientists in partnership with Ionis Pharmaceuticals discovered that an ASO drug designed to "silence" a different gene (ataxin-2) may be effective at decreasing protein accumulations that are found in almost all people living with ALS, which could be an attractive therapeutic approach for treating both inherited and spontaneous forms of the disease. NINDS is also supporting research projects that are developing next-generation ASO therapies that target the most common ALS/FTD mutation (C9orf72), and Biogen has recently started early clinical testing of such therapies. The recently established NINDS Ultra-rare Gene-based Therapy (URGenT) program will provide funding and resources to advance gene-based therapies for ultra-rare neurological diseases, including familial forms of ALS, from late-stage pre-clinical development into early clinical testing.

CLINICAL RESEARCH

Neurodegenerative disorders present unique challenges for the clinical development of interventions, including therapeutics. However, NIH research has made significant progress into developing interventions to treat and prevent neurodegenerative diseases. For example, such disorders progress along multiple stages over a span of many years. An attractive strategy is to treat as early as possible before the damage becomes widespread and nearly impossible to reverse. Because research has shown that pathologies in disorders like Alzheimer's and Parkinson's appear years or even decades prior to the onset of symptoms, the eventual goal is to effectively block the disease process before it causes neurological damage.

As a result of the substantial research advancements achieved over the last several years in understanding how Alzheimer's and related dementias develop and worsen, the drug development pipeline has never been more diverse. Thanks to increased investments in Alzheimer's and related dementias research, NIH-funded clinical studies extend beyond drug candidates that target amyloid plaques in the brain. The list of NIA-Funded Active Alzheimer's and Related Dementias Clinical Trials and Studies catalogs the many different disease pathways. Of the approximately 270 trials currently underway, more than 50 are for drug candidates to treat or prevent Alzheimer's.

In addition, NIH is leading efforts into investigating existing drugs that FDA has already deemed safe for people with other conditions—some of these drugs could be repurposed to effectively prevent or treat Alzheimer's and related dementias as well. NIA supports the Drug Repurposing for Effective Alzheimer's Medicines (DREAM) study, a collaboration with researchers at Harvard Medical School, Rutgers University, and Johns Hopkins University School of Medicine that seeks to repurpose FDA-approved drugs for dementia.

NIH-funded clinical trials also test non-drug therapies for neurodegenerative diseases. A Phase 3 clinical trial showed that deep brain stimulation (DBS) using implanted electrodes was superior to medication alone for Parkinson's disease. Ongoing research in the BRAIN Initiative continues to optimize DBS stimulus parameters and electrode technologies. A Phase 3 clinical trial of different levels of endurance exercise in people who are not yet taking medication is testing whether exercise slows the progression of Parkinson's disease.

NIH has established clinical trials networks to more rapidly test new treatments and reduce the cost of clinical research. Through NeuroNEXT, NINDS aims to support exploratory trials and biomarker validation studies that can provide more rapid preliminary testing of new treatments for neurological disorders to help identify those that merit progression to Phase 3 trials. NeuroNEXT is designed to increase the efficiency of clinical trials, facilitate patient recruitment and retention, increase the quality of neuroscience clinical trials, engage the research community in developing trials to address important questions, and enable partnerships between NINDS and industry, foundations, or academia. Investigators from NeuroNEXT have also developed a privately funded platform trial network to test industry drugs in ALS.

BIOMARKERS

Biomarkers are measurable indicators of normal biological processes, disease progression, or responses to therapeutic interventions. For example, the hallmark signs of Alzheimer's—plaques of amyloid protein and tangles of tau protein—are detected with brain imaging tests and lab tests of cerebrospinal fluid or more recently blood. By enabling researchers and physicians to see more precisely critical aspects of disease biology and response to treatment in individuals with a neurodegenerative condition, these indicators, together with development of more targeted therapies, can help get the right care to the right people at the right time.

A robust suite of biomarkers that can be measured in blood, cerebrospinal fluid, other body fluids, or tissues can help compress the timeline for developing treatments in several ways. They may:

- enable earlier identification of potential clinical trial participants, including people without cognitive symptoms of neurodegenerative disease,
- identify individuals who are most likely to benefit from a treatment,
- help researchers better understand how therapeutics work in different populations of individuals by participant stratification by disease progression/severity or underlying disease pathology,
- indicate whether a candidate drug has engaged the appropriate biological target,
- promote more accurate assessment and tracking of the impact of therapeutics in, which may be especially helpful when the time between intervention and clinical outcomes is long, and
- determine whether an underlying disease is progressing

NIH leads significant efforts to expand the development of less invasive and less expensive biomarkers for use in clinical and other settings. NIH-supported researchers continue to work to develop blood tests to detect protein clumps in the brain, including amyloid and two forms of tau (ptau181 and ptau217) to help diagnose Alzheimer's. Recent work indicates that neurofilament light chain (NfL), a component of a neuron's "skeleton," may be a promising blood biomarker that indicates neurodegeneration and could be useful for the detection of several neurodegenerative diseases. For Parkinson's disease and LBD, one of most promising biomarkers is clumped aggregates of alpha-synuclein protein that can be detected in the spinal fluid. An NIH-supported project is working on a skin test for this biomarker. Recently, the team reported detecting deposits of the protein in skin samples from people with LBD but not in healthy people, with skin test results comparable to spinal fluid tests.

In 2020, the FDA approved the first positron emission tomography scan product to detect tau tangles, which occur in neurons that later die in Alzheimer's, some forms of FTD and in chronic traumatic encephalopathy (a neurodegenerative disease caused by repeated brain injury). NIA supported a key study to validate this biomarker. Likewise, a blood test for detecting amyloid has been available in most states since fall 2020, and its development has been supported by several NIA grants, including those via the Small Business Innovation Research program.

Validating biomarkers

The promise of biomarkers depends on overcoming some key challenges. The process of validating biomarkers or demonstrating a reliable link between the biomarker and clinical benefit, is crucial, but can often be lengthy, difficult, and expensive. To accelerate the process of biomarker development and validation, NIH has established targeted biomarker programs to carry out the rigorous, focused development and validation of biomarkers that are necessary so that they may be used in therapeutic development programs, clinical trials, or clinical practice.

For example, through the MarkVCID consortium, several promising biomarkers for VCID have been developed, and soon this program will be scaled up to a second, rigorous validation phase. The NINDS Biomarker Program provides resources for discovering and validating biomarkers for all neurological disorders, including neurodegenerative diseases. There are also NIH-supported clinical trials investigating these links: the NIA-supported A4 and DIAN-TU Next Generation trials, expected to complete data collection in 2024 and 2025, respectively, have as one of their aims the delineation of connections between biomarker data and clinical outcomes.

IMPROVING QUALITY OF LIFE FOR PERSONS LIVING WITH NEURODEGENERATIVE DISORDERS AND THEIR FAMILIES/CARE PARTNERS

Neurodegenerative disorders have an enormous impact on family caregivers, long-term care facilities, health care providers, health care systems and infrastructure, and the communities in which we all live. A critical goal at NIH is to expand supports for people living with these disorders and their families and care partners. NIH has made large investments in research to improve the quality of care and care coordination. Already, research efforts have contributed to improvements in the quality of care—as well as in the resulting health, well-being, and quality of life—for those living with dementia. In addition, NIH support has enabled the development of resources designed to help ease burdens on care providers. NIA currently has more than 80 clinical trials of caregiving interventions meant for persons living with dementia or their caregivers underway.

Often, the first point of clinical care is diagnosis and referral to specialty care. Evidence suggests that cognitive impairment and dementia are substantially under-diagnosed in the general population, especially in underrepresented minorities. To address this need, NIH's DetectCID initiative is developing, testing, and validating several novel cognitive impairment assessments that are simple, culturally appropriate, and easy to administer in everyday clinical settings. This program is soon to advance to pragmatic clinical trials.

In 2019, NIA funded the IMbedded Pragmatic Alzheimer's Disease and AD-Related Dementias Clinical Trials (IMPACT) Collaboratory, which is designed to spur innovation to meet the challenges of the complex care management for people living with Alzheimer's and related dementias. Collaboratory researchers are partnering with scientists at other universities with health care and long-term care systems to test care interventions in real world settings. To date, the Collaboratory has supported multiple pilot projects and career development awards for researchers from varied disciplines. Examples of IMPACT-supported projects include:

- Working to improve dementia care management across interdisciplinary teams,
- Designing mobile apps to help adult day service centers prevent minor health issues from escalating to medical emergencies, and
- Empowering nurses in emergency departments to improve detection of dementia in patients

Assistive technologies improve the quality of life for people currently living with neurodegenerative diseases. For example, the Liftware Stabilizer is a spoon developed by an NINDS-funded small business that counteracts tremors that occur in a person's hands and helps minimize spills that can make eating in social situations an anxiety-inducing affair. Researchers funded through the NIH BRAIN Initiative are developing brain-computer interface technologies to restore the communication, mobility, and independence of people with ALS or other neurologic conditions, injury, or limb loss.

PREVENTING DISEASE

Disease prevention is typically more cost effective than treatment, and more importantly, prevention eliminates the pain and suffering associated with disease. A prime prevention target for brain health is addressing uncontrolled blood pressure.

After nearly 15 years on an upward trend, awareness among Americans about high blood pressure and how to control it is now on the decline. Even with the availability of effective blood pressure medications, many Americans are less likely than they were in earlier years to adequately control their blood pressure. CDC data has demonstrated marked health disparities in hypertension across the U.S. Moreover, Black individuals are nearly twice as likely to develop cognitive impairments and dementia as they age compared to white individuals, and recent research suggests that higher blood pressure levels in Black individuals are largely to blame for that disparity. To address this public health need, the NIH Mind Your Risks campaign educates people about the importance of controlling their blood pressure to help reduce the risk of stroke and heart attack as well as cognitive decline, including dementia. The current campaign focuses its messaging on Black men in their late twenties to early forties as they stand to benefit the most from improved blood pressure control.

Basic research now underway provides the foundation for preventing neurodegenerative diseases. For example, NIH-funded studies are exploring lifestyle and behavioral interventions, such as cognitive training, a healthy diet, and exercise, as ways to help prevent Alzheimer's and related dementias or slow

the progression from mild cognitive impairment to dementia. In early 2021, NIA released new funding opportunities to support research, including behavior change clinical trials, on the psychology of motivation, value-based decision making, and social support to help investigators develop ways to help people choose and sustain healthy behaviors over many years. There is also increasing attention to environmental factors, like stress and pollutants, in relation to neurodegenerative disorders.

CONCLUSION

We have made significant progress in understanding neurodegenerative disorders. NIH will continue to build on this momentum and advance efforts to develop effective treatments and preventions for these devastating conditions. This concludes our testimony, and we welcome your questions.