Nikolay Dokholyan, testimony to Senate Committee on Finance

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Thank you, Senators Toomey and Stabenow, for your invitation to talk to the Senate Committee on Finance, Subcommittee on Healthcare, about the emerging crisis in healthcare due to Alzheimer's disease. I am a scientist whose research is focused on fundamental and translational research in neurodegenerative diseases at the Penn State University College of Medicine. I have studied neurodegenerative disorders for over 20 years, focusing on the fundamental processes that lead to the pathological behavior of proteins in human diseases. Besides a scientific desire to understand the processes leading to neuronal degeneration, like many Americans, I have family members who have suffered from Alzheimer's disease, so I know well the emotional as well as financial toll it takes on families.

The burden that the lack of effective therapies and accessible diagnostics exerts on public health care programs like Medicare and Medicaid. This includes the fiscal burden stemming from the high costs of care for Alzheimer's patients, as well as the unstoppable erosion of beneficiaries' health as a result of the disease.

Alzheimer's disease is a progressive, irreversible, and degenerative brain disease. Patients with Alzheimer's disease suffer a range of symptoms including memory loss, dementia, confusion, aggression, and, especially at the later stages, require significant attention from caregivers. Currently, close to 8 million Americans are living with diagnosed Alzheimer's disease[1]; this number is likely a significant underestimate due to the lack of early diagnostic tools or access to healthcare[2], causing many individuals in the early stages of disease to remain undiagnosed. Currently, one in ten people older than 65 suffer from Alzheimer's disease[1], and one in three adults will be diagnosed with the disease by age 85. Women are almost twice as likely as men to develop Alzheimer's disease, even after accounting for their longer lifespan[3,4].

Among many genetic and epigenetic risk factors, age is perhaps the most critical one. As the U.S. population ages, the number of Americans with Alzheimer's disease is projected to double[1] by 2050. Today, we diagnose a new case roughly every minute; by 2050, we will be diagnosing a new case every 30 seconds. Alzheimer's disease is the sixth leading cause of death, and the fifth leading cause among adults of 65 years or older[3], meaning that roughly one in three American seniors dies from the disease. The Alzheimer's disease death toll increased a staggering 146% from 2000 to 2018, while the number of deaths attributed to stroke and heart disease, the current leading cause of death, decreased roughly 10% during this time, indicating that Alzheimer's disease in increasing importance as a public health issue. Among the top ten leading causes of

death, Alzheimer's disease is the only one that cannot be prevented, cured, or disease progression to be slowed[3,5]. These numbers, however, represent only our best knowledge, and do not accurately depict the real penetration of the disease in society. Due to the complexity of Alzheimer's disease and its manifestations, as well as gaps in scientific knowledge, the illness is often not diagnosed and attributed correctly, and so the burden in the population is likely higher than it is currently reported.

Due to the duration of the illness, disease complications, and required caregiver attention, the national cost of care for Alzheimer's patients and related dementias is a staggering $300 billion, not including the over $240 billion cost of unpaid labor from caregivers, family, and friends[3]. These numbers make Alzheimer's disease the most expensive disease in the USA. Worldwide, the annual cost of Alzheimer's disease exceeded $800 billion in 2015[6]. The projected costs of Alzheimer's disease by 2040 may exceed $500 billion[7], and by 2050 will top $1.1 trillion in the United States alone. A significant fraction of the financial burden of the disease falls on the state and federal governments through the Medicare and Medicaid programs. In 2020, these programs will cover over $200 billion of expenses associated with Alzheimer's disease. The total cost of health care and long-term care payments for Alzheimer's patients were at least three times that for beneficiaries without Alzheimer's disease. Medicaid expenses covering nursing homes and long-term care services are 23 times higher for Alzheimer's disease patients compared to other beneficiaries. Medicare and Medicaid cover close to 70% of Alzheimer's disease patients' expenses, with the remaining 30% being uncompensated, private insurance, and out-of-pocket expenses. Medicare expenses are projected to grow 400% to $589 billion by 2050, while out-of-pocket expenses will increase 350% to $198 billion. The cumulative costs between 2015 and 2050 are estimated to be $20.5 trillion. This projected financial burden is prohibitive and demands radical reassessment and prioritization of strategies to mitigate Alzheimer's disease.

The current state of the Alzheimer's disease therapeutics and diagnostic pipelines

The four principal modalities of healthcare are diagnostics, prognostics, therapeutics, and care (preventative, curative, and palliative). All of these modalities contribute to the well-being of patients and are aimed at maximizing human health and quality of life. Among these modalities, curative therapeutics would have the most profound impact on eliminating the financial burden associated with the disease, as well as the quality of life of Alzheimer's disease patients and their families. The principal challenge in identifying curative therapeutics is the current gap in scientific knowledge of the early molecular events leading to pathological disease processes, which can begin up to 20 years before disease onset. Curative therapeutics targeting disease mechanisms, as opposed to palliative therapeutics that treat symptoms, strongly depend on an understanding of the mechanisms of disease etiology, which is currently sparse. One of the hallmarks of Alzheimer's disease is the accumulation of aberrant protein deposits in patients' brains. These deposits contain protein fragments called amyloid-beta peptide or tau protein. The observation of these aggregated proteins has become the central premise for the *amyloid cascade hypothesis*[8]: that the aggregation process results in a toxic gain of function of these proteins, ultimately resulting in neuronal death. However, despite decades of research, we have not yet established the nature of this link between aggregation and toxicity, nor whether protein aggregation is indeed a driver of neuronal death or simply a consequence of some unknown

underlying processes. Nevertheless, the amyloid cascade hypothesis has been the basis for the Alzheimer's disease drug pipeline: the majority of drugs that have been developed or are currently in clinical trials target either amyloid-beta production, promote peptide clearance, inhibit aggregation, or promote neuronal resistance to aggregation. Some drugs target tau aggregates. However, no significant successes have been reported based on the strategies associated with the amyloid cascade hypothesis. Many expensive and long clinical trials have been halted at the last stages[5,9,10]: verubecestat[11], semagacestat[12], bapineuzumab[13], and solanezumab[14]. The failed drugs succeed in performing their intended functions (e.g. inhibiting BACE enzyme in case of verubecestat)[15], but these functions did not translate to the desired clinical outcomes as expected. For example, "verubecestat did not reduce cognitive or functional decline in patients with mild-to-moderate Alzheimer's disease and was associated with treatment-related adverse events"[16]. In fact, "no significant new drug for Alzheimer's has been approved in the past 14 years, despite massively expensive trials aimed at tackling the disease. The pipeline has been littered with big failures, which have come in a steady drumbeat of defeat and discouragement."[11] No preventative therapeutics exist. Although a number of palliative therapeutics are either in current clinical use or in trials, they ameliorate symptoms but do not significantly alter the course of disease. Device-driven interventions such as transcranial electromagnetic treatment (TEMT)[17], transcranial direct current stimulation (tDCS)[18], and photobiomodulation (PBM)[19] are currently being tested for palliative care.

Presently, there is no definitive clinical diagnostic test for Alzheimer's disease. Circumstantial evidence, such as family history, interaction with family members and friends, and a battery of cognitive tests suggest whether a patient exhibits signs of dementia. Alzheimer's disease is the prevalent cause of dementia in older adults, accounting for 60-80% of cases. In some cases, positron emission tomography (PET), magnetic resonance imaging (MRI), and lumbar puncture aid in confirming or ruling out Alzheimer's disease in patients with dementia. Definitive diagnosis requires histopathologic examination, which is necessarily performed only upon autopsy. Diagnosis is particularly challenging because the disease may take 20 years to manifest. By the time the diagnosis is made, pathology has already significantly and irreversibly altered the brain.

No prognostic models exist for Alzheimer's disease. Genetic markers, most notably the presence of one or two ε4 variants of apolipoprotein E[20,21], can suggest a higher likelihood that a person will develop Alzheimer's disease. However, the presence of these genetic risk markers cannot predict with any certainty the time frame for disease manifestation, nor whether the carrier will even develop the disease at all. Genetic information therefore offers potential but not definitive knowledge.

Gaps in data or understanding of the disease that are preventing therapeutic and diagnostic development

Alzheimer's disease has a complex etiology. Processes that lead to neurodegeneration arise at the molecular level and consequently result in cellular death, but physiological disease onset and consequent cognitive manifestation occurs only after massive and irreversible neuronal loss (Figure 1). As a result, neurodegenerative diseases are age-related and take from years to decades

to manifest, by which time the only treatment available to mitigate the disease is alleviation of noxious symptoms, including palliative care. The paramount challenge of developing treatments for neurodegenerative diseases lies in identifying the early pathological events that would eventually result in cell death, and targeting those events to rescue the afflicted neurons.

Molecular etiologies of neurodegenerative diseases are among the greatest mysteries and challenges in medicine. One common denominator in all neurodegenerative disease is the presence of pathological protein deposits that occur in distinct and specific regions of the brain and/or spinal cord. This common denominator has become the central premise for the *amyloid cascade hypothesis*[8]. The presence of amyloid-beta plaques and tau neurofibrillary tangles are the pathophysiological hallmarks of Alzheimer's disease, and for decades this association has fueled research focusing on the amyloid cascade hypothesis.

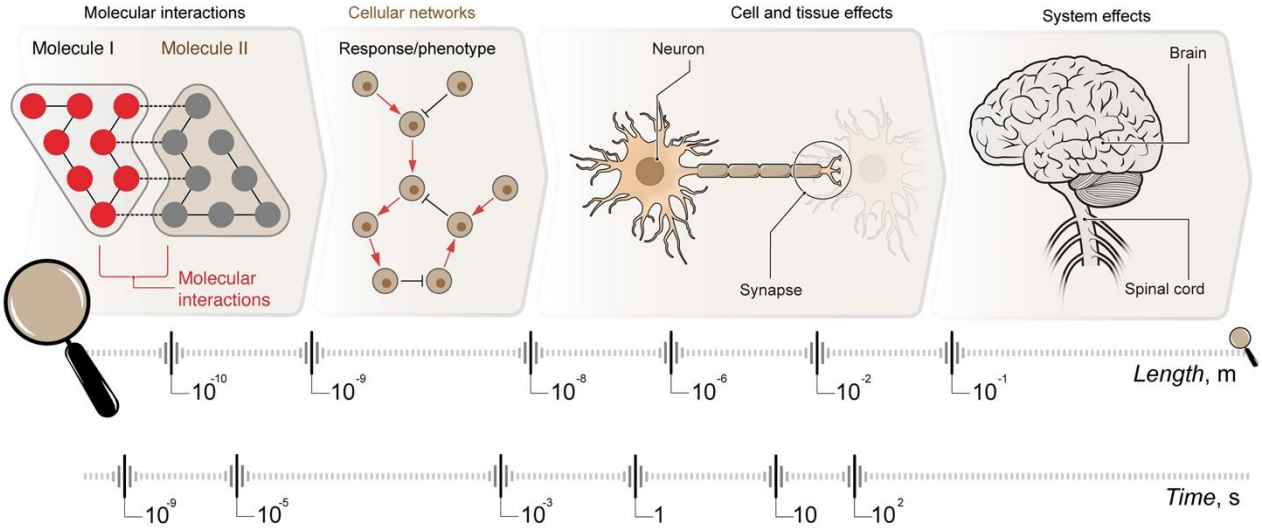

Figure 1. Multiscale processes in neurodegenerative diseases requiring translational approaches. Molecular interactions resulting in the formation of toxic species that manifest themselves at the level of cellular networks, which ultimately result in cellular and physiological phenotypes. The latter processes may take years to present as disease symptoms.

The uncertainty of whether the disease will manifest in a particular individual poses a challenge in identifying the abnormal events leading to neuron death. Identifying early pathological events is also challenging due to current technological limitations, such as a lack of precise and accurate methods for non-invasive monitoring of pathological molecular processes. A second significant limitation is our lack of disease model systems that faithfully replicate the pathology seen in human disease. The current state-of-the-art animal models, which are engineered to represent human disease in experiments, exhibit significant differences in the aging process between experimental animals and humans, as well as artifacts and biases brought about by introducing human genes into animals. These studies, therefore, require extensive validation from orthogonal studies using different methods to test the same question. Hence, we need to not only challenge the methods of interrogating the complexities of neurodegenerative diseases, but even how we design methods to approach these complexities.

Alzheimer's disease and other neurodegenerative diseases like Parkinson's disease and amyotrophic lateral sclerosis share many commonalities, such as protein aggregation, neuronal death, and the age of onset is typically in the sixties. Such similarities point towards fundamental processes common to these diseases, which are still unknown. Yet, such similarities suggest that understanding one neurodegenerative disease etiology will likely have a profound impact on understanding of other ones. As of now, neurodegenerative diseases do not have therapies that would even slow down the progression, unlike other diseases such as cancer and heart disease. No biomarkers that detect early events in the disease are established. Hence, the field of neurodegeneration needs new and disruptive thoughts and approaches to have a hope of altering their courses.

Challenges to private sector engagement in the development of therapeutics and diagnostics, and potential solutions to these challenges

The for-profit private sector is driven by deliverables, and, thus, balances knowledge of drug targets against the risks associated with them. Although Alzheimer's disease is a potentially lucrative area for the pharmaceutical and biotechnological industries, the cost associated with clinical trials and their length is a significant deterrent. The pharmaceutical industry is under significant pressure to create novel and innovative solutions and, thus, has one of the highest research and development expenditures among all industries. Despite remarkable spending on research in the pursuit of such innovation, pharmaceutical companies typically focus on already-established drug targets. These drug targets are a reflection of our fundamental understanding of disease pathological processes, an understanding that is typically established in academia. Currently, we do not have a validated model of these processes in Alzheimer's disease. Fundamental studies of basic science are prohibitively expensive to industry, which relies on academia to develop such models. Several drugs currently in the clinical trials pipeline, as well as those already approved and those that failed clinical trials, have been developed based on the amyloid cascade hypothesis and are aimed at reducing the amyloid-beta load in patients' brains. Some scientists attribute the failure of these drugs to the late timing of intervention in trials, when disease is already advanced to irreversible neuron death and consequent cognitive decline. However, evidence stemming from other fields suggest that this hypothesis needs to be revisited. For example, the research in my laboratory on amyotrophic lateral sclerosis suggests that very early events in molecular life are responsible for neuronal toxicity[22], while the large protein deposits actually serve as protective buffers against those events[23]. Deeper integration of the private sector with academia may significantly reduce the inertia in the drug pipeline and potentially offer new ideas to tackle neurodegeneration. Additionally, further outsourcing basic scientific research to academia will significantly reduce the financial burden associated with therapeutic development.

Charitable foundations are typically driven by donors' immediate need to help their loved ones. Their mission is mostly centered around research that promotes drug discovery and other short-term goals, but the resources are significantly more limited than those available to for-profit organizations. Nevertheless, these organizations have been instrumental in offering support to academia, thus providing a critical springboard for risky and innovative research. In addition,

organizations such as the Alzheimer's Association foster scientific advances not only through research but also through education and shared resources.

The failure to discover curative therapeutics for Alzheimer's disease may be a consequence of the exclusive focus on specific targets without a validated model of the molecular underpinnings of disease. Given the high rate of failure thus far, such a model is likely to come from innovative research that disrupts common thought about the disease. Hence, stimulating such research by the private sector will likely have an immense impact on our progress toward a cure for Alzheimer's disease.

Other barriers throughout the research and development process and approval process for Alzheimer's disease and potential solutions to these barriers

Federal grant programs, specifically those sponsored by the National Institutes of Health, offer support for both fundamental and translational biomedical research. At the NIH, scientific merit reviews are performed by scientists, and, therefore, offer a broad and fair coverage of research directions. These grant programs are highly competitive, and thus proposals that offer something radically different and risky ("high risk, high reward") tend to fair worse than risk-averse proposals that continue established lines of research. While the NIH has provided venues for high-risk high-return projects, they remain extremely competitive, especially for younger scientists and those with new ideas who come from outside of a traditional neuroscience background.

Protein aggregation is a hallmark of neurodegenerative diseases, including Alzheimer's disease. The mechanisms of protein aggregation are understood from a biophysical perspective, but how this molecular knowledge relates to physiology remains unknown. Thus, translational science programs aimed at marrying disparate scientific fields with clinical research are critical to establish a working model of disease. The success of translational science relies on attracting scientists with backgrounds in diverse fields to build inter-disciplinary programs. In addition, attracting industrial partners to these inter-disciplinary consortiums will facilitate their progress.

The dominant cost associated with caring for Alzheimer's disease patients stems from the extensive care required in later stages of the disease. Reducing the cost of care is mostly an untapped direction in mitigating the growing cost of the disease in the United States. Recent scientific and engineering innovations, especially in machine learning and artificial intelligence, wireless solutions, and miniature devices, may offer new and unparalleled means of caring for patients, especially in the advanced stages of the disease. For example, wearable devices with geofencing abilities may allow automated remote monitoring of a patient's health state, while location services may significantly reduce the risk of a patient with dementia wandering from home, thus allowing those with Alzheimer's disease to remain at home and out of care homes for longer. Facilitating such innovations through federal and private sector programs will have a major impact on improving the quality of care and reduce financial burden on both government programs and on individuals.

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