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Thank you, Senators Toomey and Stabenow and members of the subcommittee, for your support for Alzheimer's research and for the opportunity to testify before the Senate Committee on Finance, Subcommittee on Health Care.

Today I will address the state of Alzheimer's research, the importance of pursuing multiple approaches to treatment, the importance of fast and low-cost blood biomarkers and digital cognitive assessments, the need for greater diversity in clinical trials, the innovative Bio-Hermes study and recommendations for Congress.

For the past 40 plus years, both as an academic researcher funded by the National Institutes of Health (NIH) and subsequently leading drug development teams in the pharmaceutical industry, I have devoted much of my scientific career to trying to develop new medicines for Alzheimer's disease (AD). We have not been as successful as I would like or as successful as patients need. So far only two groups of medicines have been approved for use in patients with Alzheimer's disease. They are the cholinesterase inhibitors and one NMDA (N-Methyl-d-aspartate) antagonist; these medicines provide relatively small symptomatic improvements in patients with mild or moderate disease but do not prevent the disease or slow its relentless progression.

Currently, I am the Chief Science Officer for the Global Alzheimer's Platform (GAP) Foundation. GAP is a patient-centered non-profit organization devoted to accelerating the delivery of innovative therapies for neurological disorders by reducing the duration and cost of clinical trials. More than 85 clinical research centers across the US and Canada are part of the growing GAP Network, known as GAP-Net. GAP supports GAP-Net research sites by assisting with study start up and recruitment activities, promoting diversity in research studies and offering national programs that champion brain health and the citizen scientists who make research possible.

I joined GAP in 2015 after retiring from Eli Lilly and Company; prior to joining Lilly in 2002, I was on the faculty of the Mount Sinai School of Medicine in New York. Based on my experience both in academic research and in the pharmaceutical industry I can offer some perspectives on the work that has been done in AD therapeutics, barriers to progress and on future initiatives that could speed progress that is so urgently needed.

The first and most significant barrier to progress in developing new medicines is that we have not yet clearly identified the key biological processes causing AD. As we have learned in recent months from experience with COVID-19, once a clear causal agent is identified and characterized biologically, the search for preventative measures and treatments can proceed rationally through the conduct of highly informative basic and clinical research. For a chronic disease such as Alzheimer's with multiple risk factors and with complex pathology the path to effective treatments is quite uncertain. In the private sector, there is a high degree of interest and considerable investment in Alzheimer's disease drug development, but it is considered more risky than other therapeutic areas where the perceived likelihood of clinical and commercial success is seen as higher. This is one reason why we haven't seen the number of successful new medicines we have seen in oncology, autoimmune diseases, diabetes and other conditions.

We do know that AD is characterized by the presence of two abnormal proteins in brain, amyloid plaques and tau tangles. Many drugs designed to slow the accumulation or speed the removal of amyloid plaques have been entered into large, time-consuming and very expensive clinical trials. Some of these drugs have been shown to have potent biological effects on amyloid and it is likely that some clinical benefit may follow but much uncertainty remains. Drugs to reduce the spread of the abnormal tau protein in brain are currently being tested and their clinical efficacy remains uncertain. While these approaches may show some efficacy in some patients it is unlikely that either approach will be sufficient to prevent most cases of AD or to completely stop disease progression. It is imperative that the therapeutic value of targeting other factors associated with AD etiology and pathology be tested as quickly as possible. As examples, drugs targeting apolipoprotein E (APOE), a major risk factor for AD, brain inflammation, mechanisms of brain cell death, and neuronal activity should be developed and tested as quickly as possible. The GAP Foundation has worked over the past several years to develop a network of clinical trial sites using common processes for clinical study contracting, Ethical Review, participant recruiting and citizen engagement to help clinical sites conduct studies quickly and produce reliable, informative data.

Speeding the delivery of highly informative clinical data on promising drug candidates will require renewed effort and collaboration of government agencies, pharmaceutical companies, clinical trial sites, and, importantly, citizens willing to engage as informed and willing participants in clinical trials. Broadly speaking, academic and government investigators provide many of the insights into etiology and brain pathology that could be targeted with new medicines; commercial entities discover and provide the early evaluation of most of the viable drug candidates; pharmaceutical companies, clinical trial sites and the government funders such as the NIH then work to support the collection of clinical data, all of which can then be submitted to Food and Drug Administration (FDA) for review.

Given the complexity of AD we must expect that many clinical trials, even those testing the most scientifically promising drug candidates, will fail to show efficacy. We should not regard these as complete failures, however, since well-designed and executed clinical trials of good candidate molecules provide information that is essential for planning future drug

discovery and development activities. By testing a variety of scientifically justified approaches in efficient and well executed clinical studies and learning from each set of studies, I am very confident that we will develop effective medicines for the prevention and treatment of AD. We need to take lessons from earlier unsuccessful programs using large, expensive and time-consuming studies to identify faster and more efficient methods to test promising new molecules.

A second major barrier is the disconnect between the way patients with AD are diagnosed in current clinical practice and the way research studies identify study participants. Most practicing physicians wait and make a diagnosis of AD relatively late, when patients manifest clear symptoms and need counseling on how to manage those symptoms. We now know that the pathology of AD begins in the brain many years before patients develop symptoms such as memory loss and impairment in activities of daily living. Biomarkers, particularly PET (positron emission tomography) brain scans now enable the detection of amyloid and tau pathology well before symptoms of AD are noticeable. Many drugs in development are expected to be most effective by intervening when pathology is just starting rather than when it has advanced enough to cause major impairment. As a result, clinical trial sponsors must evaluate many potential study participants with cognitive tests and expensive, time-consuming PET scans in order to enroll appropriate trial participants; that is, participants with AD pathology but with only mild or no symptoms.

Very recently major advances have been made in the development of simple blood-based biomarkers that will speed the identification of people with asymptomatic disease both for trials and for early diagnosis in clinical practice. The development of blood biomarker tests and incentivizing their widespread use in clinical practice is very important. They will allow us to make diagnoses earlier and at a lower cost. Early diagnoses will allow for scaling up education efforts and counseling, so that families can make plans for their loved one to have the highest degree of independence possible, ideally in their own homes. Early diagnoses also will facilitate the rapid completion of clinical studies because we will identify and enroll appropriate participants in clinical trials much earlier.

The GAP foundation is in the process of standing up a platform study that will test the efficacy of more than a dozen promising blood biomarkers and digital cognitive assessments as prognostic or diagnostic indicators for Alzheimer's disease. Known as the Bio-Hermes study, it will generate biological samples and digital biomarker data from 1000 participants; the study will also enable development of a data algorithm to produce next-generation clinical trial enrollment solutions. The Bio-Hermes study will include racially and ethnically diverse participants in order to assess whether biomarker risk factors vary by race and ethnicity.

Recruiting a diverse group of informed and willing participants for an Alzheimer's clinical trial is both extremely important and challenging. Despite making up about 30% of the US population, African American and Latino people usually make up only about 3-8% of clinical trial participants. To help address this issue, GAP has committed to recruiting at least 20% African American or Latino volunteers for the upcoming Bio-Hermes study, and will not close

recruitment for this trial until we have a group of study participants that accurately reflects the community of people living with Alzheimer's disease. Our intention is for the Bio-Hermes study to be a model for building back a clinical trial infrastructure that is more efficient and gets us to a better diagnostics and medicines faster.

Of course, the Food and Drug Administration (FDA) is an essential partner to the pharmaceutical industry and academic researchers when it comes to the search for better diagnostics and treatments for Alzheimer's disease. We applaud the agency's approach to public engagement around their evaluations. We appreciate that the FDA has been transparent and energetic in its collaboration with a broad range of stakeholders, including patient advocates, researchers and pharmaceutical companies. Given the need for greater diversity in clinical trials, we hope Congress will use the Prescription Drug User Fee Act renewal process to encourage FDA to develop clear guidance on minimum standards for diversity in clinical trials.

We hope that Congress will encourage greater collaboration between FDA and the Centers for Medicare and Medicaid Services (CMS) so that future reviews regarding efficacy of new diagnostics and medicines and consideration of their merits for reimbursement can occur concurrently. This would help speed the delivery of innovative diagnostics and medicines to patients and clinicians.

Undoubtedly Alzheimer's Disease has proven to be one of the most difficult problems ever to confront biomedical researchers. I look forward to discussing how the subcommittee can take steps to speed the widespread use of blood biomarkers and digital cognitive assessments, increase the speed and diversity of Alzheimer's clinical trials, enhance investment in the AD clinical research infrastructure and encourage further collaboration between commercial sponsors, academic researchers, NIH, FDA, patient stakeholders and CMS.

Thank you.