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Chair Smith, Ranking Member Wild, and distinguished members of the Subcommittee: Thank you for the opportunity to testify before you today. It is my pleasure to appear before you today to discuss the challenges of global brain health and the importance of advancing the prevention, diagnosis, and treatment of Alzheimer's disease in the 21st century. To harness the great promise of science to mitigate the suffering of millions experiencing or at high risk of Alzheimer's disease across the globe, we need to consider rigorously not only advances in scientific knowledge but also to design the infrastructure and resources required to make this promise a reality.

I am Dr. Gladys E. Maestre, MD, PhD, Professor of Neuroscience and Professor of Human Genetics at the University of Texas Rio Grande Valley School of Medicine located on the Southern Border of Texas. I am the Director of the Rio Grande Valley Resource Center for Minority Aging Research and Co-Director of the South Texas Alzheimer's Disease Research Center. I am also UTRGV's Community Engagement Core Leader of the NIH Diversity Center for Genome Research. I am an active researcher focused on Alzheimer's dementia and related disorders in low-resource settings in the United States and in low and middle-income countries (**LMCIs**). I have conducted capacity-building activities for brain health in the Americas, including Venezuela, Colombia, Bolivia, and Haiti, and in Africa, where I have been organizing a biannual conference for more than 15 years with my colleague Dr. Raj Kalaria, in Nairobi, Kenya, to discuss research and care priorities for LMCIs and to support the development of research networks focused on dementia in Africa. I have authored several books and more than 100 peer-reviewed articles.

The National Plan to Address Alzheimer's Disease Act, known as NAPA, and the Alzheimer's Accountability and Investment Act changed the trajectory of national investments in Alzheimer's disease research, clinical and long-term care, and public awareness in our nation. These bills were recently reauthorized with the unanimous support of Congress. We are grateful to you, Chair Smith, and all the champions in Congress who have led and continue to support these bills.

What is Alzheimer's dementia, and what is the magnitude of the problem?

Alzheimer's dementia is a term for a particular group of symptoms: Difficulties with memory, language, problem-solving, and other thinking skills affecting a person's ability to perform everyday activities. Signs and symptoms progress at different rates and patterns in different people; some of them can be handled with medications or in conjunction with non-pharmacological strategies, but currently, dementia of Alzheimer's type is relentless and incurable. For the family and caregivers, Alzheimer's dementia is a source of unimaginable suffering and, even in the best of circumstances, a significant and unpredictable financial burden. By 2050, an estimated 13 million Americans will be living with Alzheimer's, and total payments for all individuals with Alzheimer's or other dementias are projected to increase to more than $1.1 trillion.

What is the difference between Alzheimer's dementia and Alzheimer's disease?

The origin of the signs and symptoms accompanying Alzheimer's dementia, mentioned above, is based in the brain. The brain changes in a relatively predictable way:

-Accumulation of beta-amyloid, a fragment of a larger protein, that acquires a particular conformation called beta-pleated sheet. The accumulation is thought to occur when there is excess production and/or defects in removing the beta-amyloid, or clearance.

-Accumulation of an abnormal protein that normally has an important role in transporting nutrients to different parts of the brain cells called neurons. They are part of the cytoskeleton, an important part of the cellular transportation system. This protein, called tau, gets abnormally phosphorylated, and basically, the railroad of the neurons gets disassembled, leading to fatal failure of the cells.

-Neurons in specific brain areas die, and then the neuronal death extends to areas that affect essential functions like sleeping, walking, and swallowing.

In brief, Alzheimer's dementia is the clinical presentation of the signs and symptoms, and Alzheimer's disease refers to specific brain changes. Although it is more common after 65, the changes in the brain are detectable 20 years earlier.

Can we diagnose dementia before symptoms appear? No, it is like diagnosing fever and there is no high temperature.

Can we diagnose brain disease before symptoms appear? Yes, it is like diagnosing an infection before there is a fever.

Can we treat the brain disease before Alzheimer's dementia appears? That is the hope that we can treat brain changes before they cause sufficient damage to detonate the signs and symptoms that characterize Alzheimer's dementia.

What are the implications of disease-modifying therapeutics?

Suppose we can treat, reverse, or stop the brain changes responsible for the presentation of dementia. In that case, it is possible that we can treat, reverse, or stop dementia, and this is the direction in which clinical trials are going.

So far, the two FDA treatments that have been approved target only the deposition of beta-amyloid. The treatments consist of systemic delivery of antibodies that attach and clear the beta-amyloid deposited in the brain. It is the first generation of disease-modifying therapeutics, but more are on the way, and they are not only focused on removing or preventing the deposition of beta-amyloid but also on tau and neuron survival or the genesis of neurons in old age.

The approved treatments are not as efficacious as expected. If brain changes are complex and only one is targeted, it is reasonable to expect that the others will continue their course, and the disease might slow down but will not be cured. This is similar to when somebody with coronary artery disease is treated with therapeutics affecting one of the risk factors, such as hypertension or hypercholesterolemia; we know that the multifactorial nature requires different therapeutic approaches -pharmacological and non-pharmacological. But they constitute an important step and a source of hope for everyone in the field.

It is also expected that the earlier we treat, stop, or reverse brain changes, the better the individual's brain health will be. Diagnosing those brain changes as early as possible is more urgent than ever.

The game-changing importance of biomarkers of brain changes

Biomarkers are detectable changes that indicate the presence or absence of a disease or the risk of developing a disease. For example, high cholesterol is a biomarker of cardiovascular health. For decades, we needed to see the brain directly through a biopsy or autopsy to be able to detect the amyloid and tau; then, we were able to see brain changes using radioligands and positron emission tomography (PET), which is a neuroimaging technique that can be used non-invasively but is very expensive and only available in high-resource settings and big academic centers.

Diagnostic tests have been developed that allow the measurement of different molecules in the cerebral spinal fluid, but still, lumbar puncture is invasive and not very appealing. What is new and very exciting is the fact that the new tests can be done in blood plasma, and a combination of panels allows the detection of species of

beta-amyloid (a ratio of beta amyloid1-42 and 1-40), abnormal tau isoforms (like ptau217) and markers of neurodegeneration, inflammation, and vascular damage.

Implications of new diagnostic and treatment approaches for low and middle-income countries LMICs

The impact of Alzheimer's dementia is significant, affecting approximately 50 million people globally, and is expected to triple to 150 million by 2050. In the African continent, Alzheimer's dementia is particularly alarming, with an expected rise from 3.6 million cases in 2020 to an estimated 16.2 million by 2050 (Belinga et al 2024).

The implementation of circulating biomarkers could potentiate the current diagnostic process, guide the selection of additional diagnostic tools, and significantly influence patient treatment strategies by contributing to the identification of suitable candidates for anti-amyloid drugs and informing the management of other neurodegenerative diseases. Utilizing circulating biomarkers can provide a more readily available approach to defining the biological aspects of Alzheimer's in Africa, and with that of African Americans and admixed populations of the United States like Black Hispanics.

We need to consider that currently, in LMICs and low-resource settings in the United States, there is inadequate healthcare coverage and imaging, neuropsychological testing are not available or are too expensive, and sometimes tools for diagnosis are not culturally sensitive or not in the language that best reflects the cognitive performance of the subject. There is also stigma and competing health and family priorities that preclude help-seeking behavior in the healthcare system.

The collective efforts of scientists across the continent under the auspices of the Africa Dementia Consortium (ADC), Alzheimer's Disease Sequencing Project (ADSP), Global Brain Health Institute (GBHI), and Africa Fingers are poised to generate comprehensive clinical and socioeconomic datasets that are crucial for improving the characterization of dementia phenotypes in Africans.

Circulating biomarkers could serve as preliminary screening tools for Alzheimer's diagnosis by identifying individuals more likely to benefit from further, more expensive, and less accessible diagnostic methods, such as CT scans or MRI, and could open regional clinical trials. However, several studies have reported that the relative importance of the Alzheimer's disease biomarkers is different for African Americans, in the sense that not only levels of amyloid have been reported to be higher in African Americans than in other segments of the population, but also that beta-amyloid levels in plasma are the best predictor of cognitive status in African Americans, while in non-Hispanic whites is tau levels. In summary, we need to learn more about factors that affect the levels of biomarkers of Alzheimer's in blood and the specific importance of these concerning severity, progression, and response to treatments. There are difficulties, a lack of health insurance coverage and the interpretation of results is derived mainly from non-Hispanic Whites.

The Maracaibo Aging Study as a source of lessons for international work on Alzheimer's disease

Together with my classmates, Drs. Joe Terwilliger and Dr. Joe H. Lee, and a team of local clinicians, we established a longitudinal study in the border city of Maracaibo, Venezuela. This is where a US-based team led by Dr. Nancy Wexler discovered the gene for Huntington's disease. We included everyone living in two catchment areas to understand aging, cardiovascular risk, cognition and developed specific phenotypes that are now incorporated in current studies everywhere like blood pressure variability in 24 h. When the Zika epidemic hit we were the first to publish the damage on the eyes of adults and not only in newborns. We developed strategies to work in humanitarian settings, instilling the values of democracy, solidarity and collaboration with the United States. It is a perfect example of why this kind of work is needed, and how it benefits the United States: community members and even public officials were touched by our American colleagues' kindness and respect towards them.

Why and how can studies in Africa accelerate discoveries in Alzheimer's relevant to US populations?

African populations are genetically and culturally variable and are woefully understudied compared with European populations. As the most genetically variable continent on earth, these populations provide an enormous yet underused resource for understanding how genetic and environmental factors interact in the etiology of all chronic (and infectious) diseases, not just brain disorders. While we have a growing African diaspora in the United States, they are still relatively few and represent but a fraction of the diversity found on the continent. To this end, it is precious to science that we engage more and more with these populations to learn more about the etiology of chronic disease in general.

I will address what I consider one of the most exciting opportunities. Genomes from Africans harbor unprecedented genetic diversity, and the potential for discovery is vast. For example, despite the steady increase in data in international repositories, high-depth whole-genome sequence data from just over 400 Africans yielded over 3 million novel, previously undocumented variants. Imagine a garden that contains many colors; if you pick some of the flowers and develop gardens in another place, the number of colors in the garden derived will be lesser than the number of colors in the parent garden. Africa is our parent garden….in the United States we only have a few colors, i.e. gene variants that are found in Africa. So, the potential health impact could benefit Africans and the global community. Consortiums like the Alzheimer Disease Sequencing Project (ADSP led by Dr. Pericak-Vance at the University of Miami and Dr. Rufus Akiyemi in Nigeria) funded by the National Institutes of Health are mining this strategy.

However, the knowledge gaps are huge, not only for the role of genetics and biomarkers but also for the role of social determinants of health, including food insecurity, forced migration, sex trafficking, infectious disorders, and economic and financial characteristics among many others, that could only be addressed with broad participation from the community, experts in social and behavioral sciences and longitudinal follow-up.

Why is important to have more inclusive studies?

The risk factors (both genetic and environmental) affecting virtually every complex chronic disease vary tremendously between ethnic groups (both due to cultural as well as genetic differences). However, most genetic epidemiology studies that have been conducted have focused on European populations for historical reasons. It is well-known in AD, that the most common genetic risk factor in European populations, ApoE, has minimal impact in African Americans and Hispanics.

Minority populations are the ones who suffer when their health risk is evaluated based on knowledge obtained solely from studies of white people. A straightforward example is milk consumption. Studies of white people showed the benefits of milk drinking in attenuating the risk of osteoporosis, for example. In the late 1990s, China started a "Drink more milk" campaign based on this science. However Chinese never drank milk historically, so there was no evidence it benefited them. It turns out that virtually all East Asian adults lack the genetic variant that allows them to digest lactose, the sugar in milk. A big problem caused by the assumption that what works for white people applies to every other population.

In studies of age-related traits like Alzheimer's Disease, this bias is even greater because of differences in life expectancy combined with a lack of trust in science in minority populations due to past abuses (like Tuskegee). Furthermore, in studying minority populations, there are difficulties in studying old folks because of immigration history (relatively recent immigration makes these populations generally younger on average and greater admixture because of the multicultural nature of the United States).

In the case of African Americans, the admixture with Europeans creates special scientific issues, which require better knowledge of the disease etiology of the ancestral source populations. But so little work has been done in Africa that we don't have this information well-characterized. This is a very important motivating factor for additional studies of African populations. Without this knowledge, we are handicapped in our ability to effectively understand the health of African American populations, which are also facing a steady increase in life expectancy.

While we expect Alzheimer's Disease to increase in frequency as African populations age (due to increasing life expectancy), this assumption is mainly based on studies of white people in the US. As those populations age, we have a unique laboratory to study this.

Well-developed and executed health studies in the developing world have the potential to win hearts and minds and change how people see the United States. We have been carrying out the Maracaibo Aging Study since 1998; we have been able to continue a research project in impoverished communities in Venezuela despite their political difficulties with the United States. Despite this project having been funded by the US government, the positive relationship we developed with the local population shows a positive view of America, as has the successful long-term collaboration with US scientists in the community (i.e. these investments benefit America because they allow engagement and make us seen as being somewhat benevolent).

What is the positioning of the United States regarding brain health in Africa?

While serious attempts have been made to transition from a fragmented strategy—a characterization of many global health programs—to a more coherent and cohesive one, still for brain health, the strategy is not cohesive, not particularly concerning Alzheimer's. In the case of AIDS, for example, the coherent involvement of the United States has been critical in public health advances since the creation of the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) in 2002, the rollout of The U.S. President's Emergency Plan for AIDS Relief (PEPFAR) in 2003, and the development of the Global Health Security Agenda (GHSA) in 2014.

The United States has made significant investments in research in Africa; in particular, the Fogarty International Center and the National Institute on Aging have played a significant role as catalyst of collaborations. However, we need to look at the role of the overall investment of the United States in the context of other large economies. For example, China has emerged as sub-Saharan Africa's largest individual country trading partner in the last 20 years. Today, one-fifth of the region's total good exports go to China. Metals, mineral products, and fuel represent about three-fifths of the region's exports to China.

China has increased its development programs around the world and, particularly in Africa. Besides investing in transportation infrastructure, higher education, and health infrastructure, China has sent more than 15,000 doctors to Africa and has treated nearly 180 million African patients, which has helped to ensure its long-term foreign policy interests in energy and food security (McGiffert, 2009).

In Africa and Latin America, China and the United States compete for economic and political influence. Investment in health research and infrastructure in Africa is a way to compete with China for influence by giving them something of value if it is done with no strings attached. As with the Maracaibo Aging Study, this has the potential to earn goodwill for the United States at a relatively low cost, in addition to the scientific benefits described above. The battle for influence in the global South is something the United States has not invested in the same degree as China over the past three decades, and while African countries fully realize China will exploit them, the infrastructure China has built is something they did not have another way to obtain quickly, so they went for it, knowing they were not given altruistically. Investment in research and health is an effective way to compete for hearts and minds, as we know from our work in Venezuela.

What models have high potential to support the leadership role of the United States in global brain health and accelerate translation to the US population?

There are several models and many ways to strengthen the leadership role in Alzheimer's research that I believe could be deployed to support more broadly global health progress. The overall notion is that efforts will benefit from a centralized and comprehensive strategy for global brain health, strengthening cooperative efforts with LMICs and targeted actions. To be sustainable, joint expertise in diplomacy and global brain health skills would be needed to draw support from appropriate health knowledge networks. A lack of this type of joint expertise has led to the deployment of technical assistance that does not leverage current infrastructure but also that is not targeted to specific geopolitical scenarios or does not account for what is needed to create new

tools and improve program delivery, advance scientific knowledge and mitigate suffering related to brain disorders.

Thinking about the education and skills needed to create a sustainable U.S. workforce with brain health and foreign diplomacy skills is essential. I believe several successful initiatives in place can be leveraged:

1.- Universities are already creating environments that support interdisciplinary education and research and blending majors to ensure cross-sector thinking and interaction. More than 250 North American universities now offer global health education. These programs are poised to enable global brain health and to cross-pollinate to harvest innovative solutions by incorporating global brain health tracks and integrating leadership and diplomacy skills in their curriculum. Programs like USAID's Higher Education Solutions Network might offer lessons on how to leverage built expertise.

2.- Expanding successful research training programs to develop new international frontiers. While there are a plethora of examples of successful research and service projects in Africa and other low-resource settings, there is a scarcity of programs that rely on building sustainable infrastructure, that includes mentoring, career advancement both locally (at the international site) and in the United States with a global health perspective.

For example, the network of **Resource Centers for Minority Aging Research** (RCMAR), supported by the Division of Behavioral and Social Research at the National Institute on Aging is a useful referent. The RCMARs have different cores to support career advancement in specific topic, like ours at the University of Texas Rio Grande Valley which is focused on Alzheimer's in Hispanic populations. The different cores supporting the research education component of the Center include the Administrative, Analysis and Community Liaison and Recruitment Cores.

3.- Supporting the research and care continuum. One successful example is the network of **Alzheimer's Disease Research Centers** (ADRCs), sponsored by the Division of Neuroscience at the National Institute on Aging, in which the research education component of individuals with high potential is supported by several cores devoted to each aspect necessary to advance knowledge, like Clinical, Imaging, Biomarker, Neuropathology, Data Management, Outreach, and Recruitment, Genomics/Genetics Cores as an example. Each of the ADRCs can incorporate and create the support cores as needed. One of the most vital characteristics is that the assessment and characterization processes of participants, their social determinants of health, and their context are standardized across the network facilitating obtaining a strong sample size.

An extension of RCMARs and ADRCs that are better positioned to carry out activities in LMICs will be a strategic step. It will create a sustainable infrastructure, empower our scientists, collaborations, and translate results to both local and abroad locations.

4.- Another example is the **Diversity Centers for Genome Research**, sponsored by the National Human Genome Research Institute of NIH. The network across the United States is focused on minority-serving institutions, each focused on specific populations and creating resources to study the admixed and original populations, such as the African or Asian Pacific populations.

All these “Center Programs” include capabilities to support career advancement, data sharing, and community engagement. Adding an international component linked will be an efficient solution.

5. The U.S.-based Alzheimer’s Association, the largest voluntary health organization dedicated to Alzheimer’s research, care, and support, hosts the Alzheimer’s Association International Conference® (AAIC®) Satellite Symposium and recently convened the dementia science community in Africa. Leaders across Africa met to discuss how advances in public health, diagnosis, and treatment can be applied within the region. This meeting is part of the year-round learning opportunities offered by AAIC and is hosted in collaboration with the Global Brain Health Institute (GBHI) and the Atlantic Fellows for Equity in Brain Health.

We are poised to think outside the box and envision a better future for all. Diagnosis, treatment, and prevention for all is a tremendous challenge in low-resource settings in the United States and in LMCIs. While today we have better treatments and prevention strategies, until we better understand a) how Alzheimer’s biomarkers are reflective of brain disease when other conditions -both medical and social- are present, and b) which characteristics of the environment are preventable risk, we need to develop as many avenues as possible. Not only do we know that we can prevent 40% of dementia by focusing on 12 modifiable risk factors, but also that enriching the environment is conducive to a higher cognitive reserve and resiliency through better architecture, multisensorial stimulation, and creativity.

Thank you very much for the opportunity to testify before the Subcommittee today and I look forward to answering any questions you may have.