House Foreign Affairs Subcommittee on Africa, Global Health, Global Human Rights and International Organizations

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Written testimony on behalf of the following witnesses from the National Institutes of Health (NIH)

Marie A. Bernard, M.D., Deputy Director, National Institute on Aging, NIH

Roger Glass, M.D., Ph.D., Director, Fogarty International Center, NIH

Good afternoon, Chairman Smith, Ranking Member Bass, and distinguished members of the Committee. I am Marie A. Bernard, M.D., Deputy Director of the National Institute on Aging (NIA), which is one of the 27 Institutes and Centers of the National Institutes of Health (NIH). I am joined by my colleague, Dr. Roger Glass, the Director of the Fogarty International Center at NIH. It is an honor to be here today to discuss NIH's efforts to stem the rising tide of Alzheimer's disease, a devastating condition and a public health issue of increasing relevance and urgency, both in the United States and globally.

An Issue of Mounting Concern

As all of us are only too well aware, Alzheimer's disease is a currently irreversible, progressive brain disease that slowly destroys memory and thinking skills and eventually even the ability to carry out the simplest tasks of daily living. In most people with Alzheimer's, symptoms first appear after age 60, although a much smaller subset of patients see onset at earlier ages. Although treatment can help manage symptoms in some people, there is currently no cure for this devastating disease. While my focus today will be on Alzheimer's disease, other forms of dementia, including frontotemporal dementia, vascular cognitive impairment/dementia, Lewy body dementia, and mixed dementias, are also important topics of research at the NIH, and I will be sharing some of our activities in these areas with you as well.

Results of a recent meta-analysis[1] indicate that 35.6 million people lived with dementia worldwide in 2010, with numbers expected to double almost every 20 years, to 65.7 million in 2030 and 115.4 million in 2050. Notably, the 2015 World Alzheimer Report estimates that 58% of all people with dementia live in low or middle-income countries.[2] In the United States alone, as many as 5.3 million people age 65 and older are living with Alzheimer's disease. Although several large epidemiological studies suggest that age-specific prevalence rates of dementia,

[1] Prince M et al., The Global Prevalence of Dementia: A Systematic Review and Metaanalysis. Alzheimer's and Dementia 9: 63-75, 2013.

[2] Alzheimer's Disease International. World Alzheimer Report 2015: "The Global Impact of Dementia." http://www.worldalzreport2015.org/downloads/world-alzheimer-report-2015.pdf

including Alzheimer's disease, are declining,[3] it is nevertheless also true that risk for the disease is greatest in the "oldest old" – those over 85. Because this age group is projected to grow substantially in the coming decades – from approximately 5.8 million in 2010 to some 19 million in 2050[4] – it is certain that unless we identify a way to prevent or effectively treat Alzheimer's, the number of affected Americans will rise significantly within the lifetime of many of us here today.[5]

The NIA-funded Health and Retirement Study (HRS), a 20-year-old nationwide survey of the health, economic, and social status of older Americans, has added a new data resource—the Harmonized Cognitive Assessment Protocol—to help advance population studies of cognitive impairment and dementia. Additional grants are funding harmonized assessments for nationally representative studies in England, Mexico, China, and India, as well as a smaller-scale field study in rural South Africa. These investments will provide unprecedented scientific opportunities for the epidemiological study of Alzheimer's and related dementias beginning in 2018. NIA also funds other initiatives to study trends in dementia prevalence and incidence around the world. Finally, we support the Integrative Analysis of Longitudinal Studies of Aging and Dementia research network, which is composed of investigators associated with over 100 longitudinal studies on aging and dementia. This initiative facilitates cross-national research on determinants and dynamics of within-person aging-related changes in cognitive and physical capacities.

Identifying Risk and Protective Factors

Identification of individuals at risk may suggest strategies for disease prevention. NIA supports a number of studies aimed at identifying at-risk individuals, including several with international reach and scope.

For example, NIA supports a study of the biomedical and socio-economic conditions that influence cognition, including susceptibility to dementia, among members of the Survey of

[3] Larson EB, Yaffe K, and Langa KM. New Insights into the Dementia Epidemic. *New England Journal of Medicine* 369: 22-25-2277, 2013.
[4] Vincent, Grayson K. and Victoria A. Velkoff. The Next Four Decades, The Older Population in the United States, 2010-2050. Current Population Reports, P25-1138. U.S. Census Bureau, Washington, D.C., 2010.
[5] Hebert LE et al. Alzheimer disease in the United States (2010-2050) estimated using 2010 census. *American Academy of Neurology* 80: 1778-1783, (2013).

Health, Aging, and Retirement in Europe (SHARE), a large and population-representative study that is harmonized with the HRS and currently deployed in 27 Continental European countries plus Israel. NIA also supports the COhort Studies of Memory in International Consortium (COSMIC), an international consortium of prospective longitudinal population-based cohorts examining the risk and protective factors for cognitive decline and the development of dementia. Established in 2012, COSMIC has developed into a consortium of 26 studies from 16 countries in five continents, with a combined sample size of >70,000, and is now uniquely placed to address some of the salient questions in relation to the epidemiology and biomarkers of neurocognitive disorders.

Identification of genetic risk factors provides insight about mechanisms that lead to development of Alzheimer's and other forms of dementia. A number of genetic loci – fixed sections of DNA that contain one or more genes – for Alzheimer's have been identified among whites of European ancestry, but the genetics of Alzheimer's among other populations is not as well understood. Investigators with the NIA-supported Alzheimer's Disease Genetics Consortium conducted a large genome-wide association study that included participants of European ancestry, African Americans, Japanese, and Israeli Arabs, and identified several loci of interest, most – but not all – of which appeared to be implicated in the disease in more than one ethnic group. These findings highlight the importance and value of trans ethnic studies for identifying susceptibility loci for Alzheimer's disease.[6]

Diagnosing Alzheimer's Disease

Biomarkers, or changes in the quantities of genes, proteins, or metabolites, whose presence in a living organism can be measured to indicate the presence of disease, are essential to the development of diagnostic techniques and treatments. As recently as 2004, there were no established biomarkers for Alzheimer's. Today, not only can we image both amyloid plaques and tau tangles (the neuropathological hallmarks of Alzheimer's disease) in the living brain, but we have also identified many other potentially promising biomarkers, from blood proteins to early changes in an individual's sense of smell. The NIA-supported Alzheimer's Disease

[6] Jun GR et al. Transethnic genome-wide scan identifies novel Alzheimer's disease loci. Alzheimer's and Dementia 13: 727-738, 2017.

Neuroimaging Initiative (ADNI), which was established in 2004 to identify and validate neuroimaging and fluid biomarkers, has contributed to much of this important progress.

ADNI is a member of the World Wide Alzheimer's Disease Neuroimaging Initiative (WW-ADNI), a global collaboration coordinated by the Alzheimer's Association to help define the rate of progression of mild cognitive impairment and Alzheimer's disease, and to develop improved methods for identifying the appropriate patient populations to participate in clinical trials. WW-ADNI also aims to standardize the methods used for conducting imaging scans and gathering and testing fluid samples so that data from all sites can be readily combined and easily understood by researchers. With participating organizations in Europe, Japan, Australia, Taiwan, Korea, China, and Argentina, WW-ADNI will allow researchers to gain a worldwide picture of the physical changes that lead to Alzheimer's disease.

Treatment

In addition to diagnosis, biomarkers can be used to track response to treatment. The Accelerating Medicines Partnership-Alzheimer's Disease (AMP-AD) Biomarkers Project is exploring the utility of tau PET imaging and novel fluid biomarkers for tracking response to treatment and/or disease progression among anti-amyloid therapies being tested in certain Phase I/II clinical trials. Screening and baseline data from the trials will be made broadly available through the Global Alzheimer's Association Interactive Network collaborative platform. Trial data and biological samples will also be shared after the trials are completed.

NIA-supported investigators are also conducting prevention and treatment trials with global reach. For example, the Autosomal Dominant Alzheimer's Disease Trial involves approximately 300 members of an extended family in Colombia who share a rare genetic mutation that triggers Alzheimer's symptoms in middle age. This family represents the world's largest occurrence of early-onset familial Alzheimer's disease. This trial focuses on whether an antibody treatment, crenezumab, can prevent or delay the appearance of Alzheimer's disease. Notably, Fogarty support enabled the University of Antioquia in Colombia to create a vivarium where rodent models of Alzheimer's have been studied and housed. Another NIA-supported initiative, the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), conducts clinical trials among individuals with the rare early-onset form of the disease. DIAN-TU

currently manages the world's first clinical trial to prevent development of Alzheimer's in families at genetic risk of early-onset disease. This groundbreaking trial is being performed at sites in the United States, Canada, Australia, and across Europe.

DIAN-TU investigators also manage the DIAN Expanded Registry (DIAN EXR), an international research registry for individuals with early-onset Alzheimer's and those known to be at risk. Patients and family members enrolled in DIAN EXR can learn about current research and clinical trials, gain access to genetic counseling and testing, and attend international family conferences that will enable them to connect with scientific and medical experts as well as other families affected by this devastating condition.

International Collaboration

In an interconnected world, it is essential that NIH continue to invest in a research workforce that can respond to evolving challenges that affect us all. As demonstrated in the Colombian trial example, these discoveries are often made by U.S. and foreign scientists working in close collaborations that enable the best and brightest minds to tackle complex health challenges together.

Through its Global Brain Disorders Research program, Fogarty also provides opportunities for investigators to conduct research specifically on nervous system function and impairment, including Alzheimer's disease. In partnership with 10 other NIH Institutes and Centers (including NIA), this program supports international collaborative research relevant to low- and middle-income country settings.

NIA remains committed to speeding the pace of global research by large-scale sharing of data with qualified researchers around the globe. For example, ADNI data have been widely available since the initiative's establishment, and data from AMP-AD and the Alzheimer's Genetics Consortium are also made available to investigators worldwide. Data from the HRS and its sister studies in other countries are likewise freely available without any embargo period.

The International Alzheimer's Disease Research Portfolio (IADRP), developed by the NIA in collaboration with the Alzheimer's Association, enables public and private funders of Alzheimer's research to coordinate research planning, leverage resources, avoid duplication of funding efforts and identify new opportunities in promising areas of growth. Currently, the

database contains information about over 8,300 unique projects representing over 30 funding organizations in 11 countries.

Alzheimer's disease and related forms of dementia devastate families in every corner of the world. At the National Institute on Aging and the Fogarty International Center, it is our hope that through cooperation and coordination with our partners around the globe, we will make much-needed and long-anticipated progress in finding a prevention or a cure.

This concludes my testimony. I welcome the opportunity to answer your questions.