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Aging for the hearing:

“The Arc of Alzheimer’s: From Preventing Cognitive Decline in
Americans to Assuring Quality Care for those Living with the Disease”

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Thank you Chairman Collins, Ranking Member Casey and members of
the Committee for the opportunity to testify today before the Committee
about one of the most important issues of our time, Alzheimer disease.
My name is Kristine Yaffe, M.D. and I am Professor of Psychiatry,
Neurology and Epidemiology at University of California, San Francisco
in San Francisco, California. I am also a physician and Chief of
Neuropsychiatry at the San Francisco VA Medical Center and am a
member of the Medical and Scientific Advisory Committee of the
Alzheimer’s Association.

Alzheimer disease is a brain disease and the most common form of
dementia, a syndrome of cognitive changes usually associated with
aging. Alzheimer’s results in memory and other cognitive symptoms

from a complex accumulation of abnormal proteins (including beta-amyloid and tau) in the brain that in turn leads to death of neurons. Despite tremendous advances in fundamental brain science over the past few decades, there is still much to learn about this process. It is unclear why some people get the disease and others, who have may have evidence of the protein accumulation, may not. Furthermore, despite great effort, we still do not have very effective treatments.

What we do know for sure is that Alzheimer disease is devastating. It carries tremendous toll on the patient, caregiver, our health care system and society. Alzheimer disease is also the sixth leading cause of death. We also know that because our society is aging and Alzheimer's is an age-related disease, it will grow exponentially and with that, the cost and burden will skyrocket. Even now, Alzheimer's has grown to become the most expensive disease in America with more than two thirds of this cost paid by Medicare and Medicaid. By 2050, the number with Alzheimer's are expected to triple, and the associated costs will quadruple to \$1.1 trillion per year unless we can change this trajectory through the development of effective treatments and prevention.

One of the most important conceptual changes in the field is that it takes decades for the abnormal proteins to accumulate in the brain before any clinical symptoms. Therefore, it may be possible to intervene early, even before symptoms, and prevent or delay Alzheimer disease. It is increasingly possible to identify those at higher risk based on genetics, early symptoms and detection of the protein accumulation. Thus, we are

finally in a position to study if prevention is possible. This has evolved into two very important strategies 1) studies of risk factors that may be modifiable and 2) studies of new investigational drugs for people at risk but without symptoms.

There is emerging evidence that several factors may increase the likelihood of developing Alzheimer's in addition to genetics. Many of these risk factors may be "modifiable" and good targets for both individual and public health strategies.

One of the things we have learned is "what is good for the heart is good for the brain." The reason for this is that traditional risk factors for heart disease including hypertension, diabetes, and high cholesterol, are also associated with about a 50% increased likelihood of developing Alzheimer disease and vascular type of dementia. The exact mechanisms still need to be worked out but most likely result from effects on the brain blood vessels as well as greater amyloid accumulation. There are several trials underway assessing if certain diabetes and cholesterol medications and blood pressure control may protect against developing cognitive impairment. We need more research to understand how treatment of cardiovascular factors may benefit brain health. It is also key to understand when is the best life stage to address these cardiovascular factors with some evidence supporting that mid-life or even earlier is the best time to intervene.

The concept of cognitive reserve has been proposed as an explanation for why some people are able to tolerate the brain changes associated

with Alzheimer's and other dementias without exhibiting symptoms. Animal studies indicate that certain factors inhibit or promote the brain's capacity to generate new neurons, even in adulthood, and that this "plasticity" of the brain underlies cognitive reserve. This is a very exciting concept as it suggests that there may be strategies, even in late life, to promote resistance to Alzheimer disease. Factors that contribute to cognitive reserve include physical activity and cognitive stimulation and education. Several studies, both observational and trials, support this idea that being more "active" both in body and mind, may prevent cognitive aging and Alzheimer's. More work is needed to test this strategy and make definitive conclusions for prevention.

Traumatic brain injury (TBI) is a common condition that peaks in early adulthood and again in late life. Many studies have reported that moderate and severe brain injury increases the risk of dementia; however, the mechanisms for this still need to be worked out. Recently there has been great interest in mild TBI (often called concussion) but there are only a few studies of mild TBI and risk of dementia and the results are controversial. This is a very important area for investigation given how common TBI is and how it can affect people across all ages.

An area of recent discovery has been the connection between sleep quality and risk of Alzheimer disease. This is a fascinating area of investigation as research suggests that during sleep, especially if adequate, proteins are "cleared out" of the brain. Therefore if sleep is disrupted due to sleep apnea or insomnia, the proteins such as amyloid may accumulate and lead to greater chance of Alzheimer's. Few studies

have investigated if better treatment of sleep disorders might improve cognition and even delay Alzheimer disease but many are interested in exploring this line of investigation.

Many people want to know about diet and if certain diets may prevent Alzheimer's. There is still a lot we do not understand but it seems unlikely that individual vitamins, nutrients or foods are related to brain health unless someone is deficient in that substance. More compelling has been the idea that a dietary pattern, such as the Mediterranean diet (rich in vegetables, fruit, fish, nuts, olive oil), may be advantageous to both heart and brain health but studies have not been conclusive.

Some argue that these modifiable risk factors will not ever "cure" Alzheimer's disease. For that it is clear we need better drugs. However, because these lifestyle factors are so common and can be changed (without side effects), they could have a big effect on both the individual and society. Studies suggest if people could reduce these risk factors by a modest amount (for example do 10-25% more physical activity or lower hypertension by 10-25%), we could see a big effect on the downstream number of people that develop Alzheimer's over time. Furthermore, we need to study these factors in combination. Many countries have conducted multidomain trials in which several of these factors are addressed in combination and preliminary results look promising. It would be very important to conduct such trials in the US.

There has also been tremendous interest in developing more effective drugs for Alzheimer's and seeing if these may prevent the disease. In the US, there are four ongoing pharmacological trials testing possible prevention of Alzheimer's for people at risk for the disease (genetic risk or evidence of amyloid build up) but without any symptoms: the Dominantly Inherited Alzheimer Network Trials Unit trial, the Alzheimer's Prevention Initiative, Autosomal Dominant Alzheimer's Disease trial, and the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Study. These trials are critical in order to identify better treatments as early in the disease course as possible. Most of them target the accumulation of the abnormal proteins. In this way, it may be possible to prevent or delay the disease. Many are optimistic that this approach will be high yield.

Some experts, including myself, think that some day, Alzheimer's will be like chronic heart disease with several available drugs that treat different aspects of the disease. It will not be the devastating diagnosis it is today but something that can be effectively slowed and treated. In addition, these drugs will be combined with lifestyle modifications such as cardiovascular health, physical activity and cognitive stimulation. Clearly in order to achieve this, we need more research. While the field has come a remarkably long way from when (just a few decades ago) dementia was considered a normal part of aging, we have a long way to go in order to effectively treat and prevent Alzheimer's.

In 2011, the bipartisan National Alzheimer's Project Act, that you

Chairman Collins co-authored, became law requiring the creation of a National Alzheimer's Plan. The U.S. Department of Health and Human Services released this plan in 2012 with the main goal to prevent and effectively treat Alzheimer's by 2025. In 2014, Congress enacted the Alzheimer's Accountability Act that requires the National Institutes of Health (NIH) to prepare for Congress and the President an annual professional judgment budget or bypass budget. In the bypass budget for Fiscal Year 2018, NIH Director Francis Collins has stated that the NIH will require an additional \$414 million in funding to remain on track to achieve the Plan's 2025 goal. I urge you to act in order to make this happen.

Thank you for your interest and time and all that you do.