

**Testimony of Dr. Rudolph Tanzi
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Promoting Healthy Aging: Living Your Best Life Long Into Your Golden Years
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I want to thank Chairman Collins, Ranking Member Casey, and other Members of the Special Committee on Aging, including Senator Warren from my home state of Massachusetts, for the opportunity and privilege of discussing the role of genetics and lifestyle in promoting healthy aging into our Golden Years.

My name is Rudolph Tanzi. I serve as the Joseph P. and Rose F. Kennedy Professor of Neurology at Harvard Medical School and Vice-Chair of Neurology and Co-Director of the McCance Center for Brain Health at Massachusetts General Hospital. I also serve as Director of the Alzheimer's Genome Project supported by the Cure Alzheimer's Fund, one of the highest impact Alzheimer's disease research foundations in the world.

I have dedicated my entire career to studies aimed at preserving and promoting brain health and preventing brain disease. Over the past four decades, I have discovered and characterizing numerous genes influencing susceptibility for Alzheimer's disease, including the first three. I have used knowledge gained from these genes to develop new therapies for treating and preventing Alzheimer's disease. Some of these new drugs are already in clinical trials in Alzheimer's patients. I have also published over 500 original research papers on Alzheimer's disease and brain health and have written three best-selling lay-level informational and self-help books on brain health, genetics and immunity.

I will focus my remarks today on how we can best maintain brain health and resilience against age-related diseases, including neurological diseases such as Alzheimer's disease, as well as other chronic diseases including diabetes, heart disease, and cancer. Approximately 8 in 10 older adults in the United States have a chronic disease, and 7 in 10 have two or more. Chronic diseases are the leading cause of death and disability and the leading drivers of the nation's \$3.3 trillion in annual health care costs. Alzheimer's disease, the most common form of dementia in the elderly, currently affects nearly six million Americans. The cost of this disease to our country is approaching 300 billion dollars per year. Half of Americans over 85 years old exhibit Alzheimer's symptoms, 2/3's of which are women. With the American lifespan now up to nearly 80 years, this disease is a burgeoning epidemic that could someday single-handedly collapse our healthcare system.

As modern medicine has extended lifespan, unfortunately, our healthspan has not kept up, resulting in rampant increases in the incidence of age-related diseases. How can we stem the tide of Alzheimer's and other chronic diseases? The research is promising and turns traditional notions about disease upside down. Not too long ago, we were taught that the effects of the genes you inherited from Mom and Dad are fixed and unchangeable. But new research, in the burgeoning field of epigenetics has demonstrated that the activity, or, as we call it, the "expression" of our genes is fluid, dynamic, and responsive to everything we do and think.

Every choice we make leads to experiences that change the expression of our genes. Gene expression is actually controlled by our habits. A healthy lifestyle of good habits leads to beneficial gene programs and good health. The opposite is also true, You may currently have bad habits, like a little too much junk food, which induce gene expression programs that promote risk for age-related disease. But, with repetition, the establishment of new, "good habits", like a plant-rich diet, will change gene expression programs that promote health. I wrote about this at length in my books "Super Genes" and "The Healing Self" At the end of the day, by altering our gene expression programs through our daily conscious choices, we have the power to slow the aging process, improve mood, staving off anxiety and depression, reduce persistent aches and pains, improve quality of sleep, and even decrease risk or age-related chronic diseases including cancer and neurodegenerative diseases.

Besides the nearly 6 million currently afflicted with Alzheimer's dementia, it is estimated that another 30 million Americans harbor brain pathology, such as amyloid plaques and tangles, that substantially increases their risk for symptoms of dementia over the next 5-15 years. Like heart disease and diabetes, Alzheimer's disease actually begins a decade or more before symptoms arise. We routinely diagnose other age-related diseases prior to symptoms, by checking, for example, blood cholesterol and glucose levels, and then treating them early on to prevent onset of symptoms. However, we do not diagnose Alzheimer's disease until a patient's brain has already degenerated to the point that it causes cognitive dysfunction and dementia. And, worse, clinical trials aimed helping these patients treat the brain pathology, such as plaques and tangles that, based on brain imaging studies, had initiated the disease a decade or more before symptoms. Treating these pathologies in patients with dementia is simply "too little, too late". Thus, trial after trial has failed. Going forward, we will need to treat this disease following a mantra with which the Cure Alzheimer's Fund was founded: "Early prediction, detection, early detection, early intervention".

In the future, we will therapeutically address Alzheimer's disease by first determining one's genetic risk based on family history and polygenic risk scoring, and then use this information to guide *when* early detection of pre-symptomatic disease pathology, with, for example, brain imaging blood tests, should first begin, certainly no later than 50 years old. Once the earliest signs of brain pathology are detected, therapeutic intervention would be warranted, similar to how we take a cholesterol drug to stave off heart disease. Unfortunately, analogous drugs for Alzheimer's disease are still in development, but should be available for early intervention in the future.

Importantly, the successful development of preventative drugs will require innovative and progressive thinking by the FDA that would allow trials and potential approval of drugs that can reduce early initiating brain pathology in a pre-symptomatic person, even if they do not reverse symptoms of dementia. If such a drug were sufficiently safe, it could be approved for use in early prevention in at-risk individuals. We would then rely on “real world evidence” to determine whether the drug reduces the incidence of symptomatic Alzheimer’s disease over the next 5-10 years. This prevention strategy is in line with the FDA draft guidelines for Alzheimer’s released in February 2018. But, now we must push the FDA to see them enacted. Otherwise, the alternative is 10-year prevention clinical trials aimed at the early initiating Alzheimer’s pathology, such as plaques and tangles, and then waiting to see if dementia is averted. Such prevention trials are highly unlikely given the prohibitive cost of many billions of dollars and limited patent life.

While we wait for effective drugs, we must in parallel consider whether we can stave off Alzheimer’s via lifestyle and behavioral interventions. Along these lines, the genetics of Alzheimer’s disease, for example, exhibits a clear dichotomy. On one hand, we first discovered gene mutations in three genes that virtually guarantee early-onset familial Alzheimer’s disease. Fortunately, these *fully penetrant* gene mutations account for only 3-5% of Alzheimer’s. Meanwhile, while we have also found over 30 genes associated with risk for sporadic Alzheimer’s disease. In contrast, their mutations do not guarantee the disease in the span of a normal lifetime. So, lifestyle interventions *will* make a difference in over 95% of those at risk for Alzheimer’s disease. In support of this statement, a large study was recently published by Lourida et al. in JAMA (2019), that concluded: “A favorable lifestyle was associated with a lower dementia risk [even] among participants with high genetic risk.”

The same is true for other age-related chronic diseases. It is generally the case that on common, age-related, complex genetic disorders such as Alzheimer’s disease, heart disease, diabetes, that only 3-5% involve genetic mutations that guarantee disease (fully penetrant) and that 95-97% involve genetic factors that are modifiable by lifestyle.

I will now conclude with brief recommendations for lifestyle that have the potential to reduce age-related chronic diseases. These factors in particular have been shown to prevent the three major hallmarks of Alzheimer’s-related brain pathology: plaques, tangles, and neuroinflammation. For this purpose, I have created the acronym, SHIELD, which has now been featured frequently in popular media, for example on the NBC Nightly News and just this past weekend on the Today Show.

S stands for 7-8 hours sleep, which serves to clear away Alzheimer’s pathology.

H is for handling stress, for example, with a meditation practice.

I is for interaction with friends. Loneliness increases risk for Alzheimer’s by two-fold.

E is for exercise, which induces new nerve cell growth to strengthen brain regions affected in Alzheimer's disease.

L is for learning new things, which increases the number of synapses in your brain, the connections between nerve cells storing your memories. Synapses loss correlates most with the degree of dementia. The more you make, the more you can lose, before you lose it.

D is for diet. The best diet for the brain is the Mediterranean diet, which minimizes red meat and is rich in fiber from fruit and vegetables that strengthens bacteria in your gut, or your gut microbiome. And, by the way, a healthy gut microbiome has been shown to reduce brain neuroinflammation, the biggest killer of nerve cells in the brain.

In summary, while we await the medicines that will prevent and treat Alzheimer's disease, it is my hope that research will be accelerated on lifestyle interventions. I also hope that we can pro-actively educate the American public about using plans like SHIELD to improve their brain health and reduce risk for brain disease. We should also let the American population know that despite their family history and personal genetics, in the vast majority of cases, lifestyle and behavioral changes have the potential to preserve and promote brain health and prevent age-related diseases – not only Alzheimer's, but also heart disease, diabetes, heart disease and cancer.

Thank you for your attention.