

Scientists say national Alzheimer's plan milestones must be strengthened to meet goal by 2025

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The U.S. Government has initiated a major effort to prevent and effectively treat Alzheimer's disease by 2025. However, a workgroup of nearly 40 Alzheimer's researchers and scientists says the research milestones in the U.S. Government's National Plan to Address Alzheimer's Disease must be broadened in scope, increased in scale, and adequately funded in order to successfully achieve this goal. A series of proposals by the workgroup to enlarge and strengthen the Plan are published today in *Alzheimer's & Dementia: the Journal of the Alzheimer's Association*.

According to the authors of the newly published article, who include U.S.-based academic and industry scientists across all disciplines of Alzheimer's research, "Many prominent investigators believe the prospect of delaying the onset of disabling symptoms within a decade is an attainable goal, provided we can surmount several scientific, administrative, and most importantly, financial impediments." The authors continue, "Inadequate funding remains the single most important impediment to progress in achieving the research goal of the National Plan."

There are more than 5 million Americans currently living with Alzheimer's at a cost to the nation of \$214 billion, according to the Alzheimer's Association 2014 Alzheimer's Disease Facts and Figures report. With Americans living longer than ever before, these numbers

are set to soar to as many as 16 million people living with Alzheimer's [disease](#) at an unsustainable cost to the nation of \$1.2 trillion by 2050.

"We are a scant 11 years from the 2025 goal of the Plan, and we have no time to lose," said Maria Carrillo, Ph.D., Alzheimer's Association vice president of Medical and Scientific Relations and a co-author of the article. "We commend the U.S. National Institute on Aging for creating the original milestones that have been incorporated into the Plan, and for committing to revising these milestones regularly. Further, the NIA has created an excellent opportunity to update these milestones in conjunction with its Alzheimer's Disease Research Summit to be held in February 2015. While our workgroup does not believe the milestones, as they currently stand, are sufficient to reach the 2025 goal, if the suggested updates are swiftly implemented and funded we believe prospects for being able to prevent and effectively treat Alzheimer's by 2025 will increase dramatically."

"This article is the voice of leading scientists recommending what needs to be incorporated into the Plan's milestones now to prevent and effectively treat Alzheimer's and other dementias," said William Klunk, M.D., Ph.D., chair of the Alzheimer's Association Medical and Scientific Advisory Council and a co-author of the article. "The suggested milestones outlined in the article identify significant increases in the scope and scale of Alzheimer's research, which would bring Alzheimer's research efforts more closely into line with the scale of activity needed to make substantial progress against other major diseases like Cancer and HIV/AIDS. The proposed revisions are meant to ensure that the National Alzheimer's Plan's milestones outline an adequate level of both the types and amount of research that are needed to achieve the 2025 goal."

Klunk is a Distinguished Professor of Psychiatry and Neurology at the University of Pittsburgh School of Medicine in Pittsburgh, PA. He is

also the Co-Director of the Alzheimer's Disease Research Center at the University of Pittsburgh.

New and Revised Milestones from the Workgroup

The National Alzheimer's Project Act (NAPA) was signed into law in 2011, calling for the development of the country's first-ever National Plan to Address Alzheimer's Disease. The Plan, released in 2012, outlined a set of initiatives to provide improved tools for doctors, assist caregivers and individuals with Alzheimer's and other dementias, raise public awareness about the disease, and advance research. It set an aggressive research goal to "Prevent and Effectively Treat Alzheimer's Disease by 2025."

A variety of strategies were created, including identifying "research priorities and milestones." The U.S. Department of Health and Human Services approved a set of interim milestones in 2013 to provide a roadmap toward achieving the Plan's 2025 goal.

In June 2014, the Alzheimer's Association convened an expert workgroup to evaluate the milestones, determine whether the field is on track to achieve them, recommend changes in the parameters of the milestones, identify unaddressed gaps, and recommend additional milestones to fill these gaps. The workgroup consisted of world-renowned experts in Alzheimer's research and policy.

One goal of the workgroup was to stimulate thinking about the Plan milestones at the upcoming NIA Alzheimer's Disease Research Summit and thereby enhance the discussion that will occur.

The recommendations in the newly-published article make it clear that, in order to meet the Plan's 2025 goal, the research effort for Alzheimer's disease must be enlarged in scale, expanded in scope, and better

coordinated. According to the authors, what is needed are:

- More clinical trials, testing more drugs - and more non-drug strategies - against more targets, involving more people and more diverse populations, aimed at treating and preventing more types of symptoms.
- More basic research to discover and validate additional biomarkers and uncover new therapeutic targets.
- And a stronger research system and infrastructure with more data sharing and collaboration, conducted in a more interdisciplinary manner with increased emphasis on research to identify and translate effective treatments to medically accepted and widespread use.

The authors suggest revisions to a majority of the existing Plan milestones, and propose 25 new milestones. Those of greatest urgency and highest potential impact are in drug development, risk reduction, and new conceptual models of Alzheimer's.

Drug Development

Six current milestones focus on developing novel targets into effective treatments. The expert workgroup supported the overall goals of these milestones, but commented that history shows that only about 13% of new drugs make it from the preclinical stage to Phase III trials.

- This suggests that to achieve the stated success criteria, approximately 23 drugs and/or targets would need to be identified, characterized, and validated. The current milestone only calls for six.
- In fact, because novel targets need to be identified across many pathways and mechanisms (e.g., reducing amyloid, reducing inflammation) the workgroup suggests that, in reality, a much

larger number – 60 – will likely need to be identified.

- The expert workgroup recommends that the numbers and projected costs in these milestones be adjusted to more accurately reflect the reality of drug development.

Current milestones concerning the development of drugs against known targets call for initiation of three to six Phase II drug trials, at least two of which should be in asymptomatic subjects.

- The workgroup says, "given the high attrition rate in Phase II trials to date, to achieve the success criteria ... perhaps 12 or more trials will need to be initiated. ... The milestone also calls for trials of agents against three to six therapeutic targets, so these trials will need to involve targets beyond amyloid." These targets could include tau, inflammation, and nicotinic agonist receptors, according to the article.

Current milestones call for initiation of Phase III trials against at least three known targets, with at least one of these trials in asymptomatic, at risk subjects. Currently, four asymptomatic Phase III trials are already underway.

- The authors suggest that the milestone be revised to reflect the large number of Phase III trials that will need to be initiated to achieve three successful trials, and that at least one trial should be of a symptomatic therapy.

Risk Reduction

Epidemiological studies have provided important information about the many possible exposures that influence the risk of developing Alzheimer's and other dementias. These include genetic, vascular, psychosocial, dietary, and other lifestyle factors. The utility and

importance of epidemiologic studies have been confirmed with the recent success reported at the 2014 Alzheimer's Association International Conference of an early analysis of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) multidomain prevention trial. All the factors used as part of the intervention in this trial—diet, physical exercise, cognitive training, social activities, and control of vascular risk factors—were identified through epidemiologic studies. However, more resources must be committed to epidemiological infrastructure and studies to fully harness the power of this methodology.

- The expert workgroup calls for, among other things, a reframing of the Plan milestones to focus more broadly on risk issues and prevention of cognitive impairment and dementia across the entire lifespan. Studies generated to meet these milestones should be attentive to changing demographics and ethnic and racial shifts in the population, and should have harmonized data collection methods.
- The workgroup further recommends the initiation of a large, multidomain prevention trial focused on modifiable risk factors in the United States to replicate the results of the FINGER trial in a larger, more diverse population.

New Models

Given that current approaches to treatment have not yet resulted in effective new therapies, strategies are needed to re-examine existing paradigms and consider new conceptual models of Alzheimer's. The Alzheimer's Association convened Research Roundtables in 2006 and 2012 to explore mechanisms other than the dominant amyloid hypothesis that may contribute to neurodegeneration in Alzheimer's. Pathways identified that may offer additional therapeutic targets include those associated with aging, such as synaptic loss, decreased neurogenesis, cell

death through internal mechanisms, and insulin resistance; and cell cycle events and other cellular processes such as inflammation, mitochondrial dysfunction, and alterations in various proteins.

Among the barriers to exploring these alternative hypotheses has been a lack of tools, infrastructure, and resources, especially for basic science and pre-clinical research. Recommended new research milestones for this area include:

- Creation of several mechanisms for funding a substantial training and research program on the basic biology of aging, vulnerabilities and diseases of the brain and nervous system, and the biological underpinnings of "super-aging."
- Convening a "think tank" to reexamine conceptual models of Alzheimer's disease beyond amyloid.

Provided by Alzheimer's Association

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