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Penn physician argues for 'meaningful' update to national Alzheimer's act

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A key strategy missing from the ambitious Alzheimer's disease plan signed into law by President Obama six years ago could send investigational drugs down a precarious pipeline, argue two physicians from the Perelman School of Medicine at the University of Pennsylvania and the University of Michigan in *JAMA Internal Medicine*. The National Alzheimer Project Act (NAPA) calls for new treatments to slow or prevent the disease by 2025, but as it stands now, there's no strategy in place to determine whether the interventions being studied today have a so-called "meaningful" clinical benefit for patients. Without that strategy, private interests could shape how a drug's clinical benefit is established after approval and therefore costs, similar to what's happening in the oncology world.

Authors Jason Karlawish, MD, a professor of Medicine, Medical Ethics and Health Policy, and Neurology at Penn and co-director of the Penn Memory Center, and Kenneth M. Langa, MD, PhD, associate director of the Institute of Gerontology at the University of Michigan and Veterans Affairs Ann Arbor Healthcare System, argue their case and suggest approaches to improve the NAPA in a viewpoint titled, "Unfinished Business in Preventing Alzheimer's Disease."

The first goal of NAPA aims to slow or prevent the disease altogether, with five promising clinical trials underway today. However, only one of those trials, which is investigating the use of CAD106 and CNP520 (an immunotherapy and an amyloid enzyme inhibitor), employs measures to determine whether the intervention is deemed clinically beneficial, or

evidence of impact on day-to-day function. The other trials evaluate the disease course using a measure of cognition called an intermediate clinical endpoint, which is a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit. It's a legal measurement that falls under the US Food and Drug Administration's accelerated approval program. Developed initially in response to public demand to speed HIV treatments, the program permits this evaluation strategy for serious and life-threatening diseases, such as Alzheimer's, the sixth leading cause of death in the United States that affects 5.4 million Americans today. If approved by the FDA, it can get life-saving drugs to patients faster.

However, once that approval occurs, the agency expects the company that owns the drug to collect evidence to demonstrate the drug's clinical benefit.

That's an undesirable path that should be improved upon in order for this plan to be more successful, Karlawish said."NAPA is missing an important strategy," Karlawish said. "We need a strategy for gathering and interpreting information and data to determine if it shows a meaningful clinical benefit to patients - before the FDA approves the drug."

"Alzheimer's is a complex, unique disease that needs more a rigorous and expanded set of study endpoints in order to better quantify outcomes," he added.

To determine if the interventions being tested in trials have a clinical benefit, three questions should be asked, the authors wrote: Is there a slowing of the trajectory of cognitive decline after the onset of dementia? Does treatment lead to a lengthening of the mild or severe stages of dementia? Does treatment delay death and, if so, is treatment associated with compression or expansion of the time living with

dementia?

Karlawish and Langa propose that participants in Alzheimer's prevention studies should also participate in long-term observational cohort studies, where functional outcomes can be evaluated and analyzed alongside cognitive test results.

"These studies are one way to address the very high cost and difficulties of getting a read on long-term outcomes, and exemplifies collaboration in the area of data sharing, a strategy emphasized in the Alzheimer plan," Langa said.Karlawish explained that issues of competing interests must also be addressed. After approval, a drug will be marketed under a brand name, and the public and private interests and resources will begin to diverge.

Such a path could have the same controversial downstream effects seen in the oncology world, where pharmaceutical companies shape the evidence that establishes whether a medication has a meaningful clinical benefit, and therefore it's price, the authors said.

"Claims that these treatments have significant clinical benefits will engage both public and private interests, which can be at odds," Karlawish said. "We think the U.S. Advisory Council on Alzheimer's Research, Care, and Services is the right place for establishing a common set of publicly recognized guidelines for the design and interpretation of studies to establish the benefit of an Alzheimer's prevention therapy."

Provided by Perelman School of Medicine at the University of Pennsylvania

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