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## Unfinished Business in Preventing Alzheimer Disease

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**By law, the United States** has a plan to address Alzheimer disease.<sup>1</sup> The first of the National Alzheimer Project Act's 5 goals is the discovery by 2025 of interventions that prevent and effectively treat the disease. The eTable in the Supplement summarizes 5 current prevention trials, most supported jointly by the National Institutes of Health and pharmaceutical companies.<sup>2</sup> This alignment of public and private interests, shared resources, and the willingness of thousands of cognitively normal adults with heightened genetic or biomarker risk of Alzheimer disease to enroll in trials are signs of progress. The plan is missing an important strategy, however.

The aim of the medications being tested is to prevent, or significantly delay, the onset of symptomatic Alzheimer disease. Only 1 of the 5 trials, however (Generation; NCT02565511), uses measures of symptomatic disease or function as a coprimary end point. Instead, most use only a measure of cognition, called an "intermediate clinical end point" because it does not establish meaningful clinical benefit.<sup>3</sup> The US Food and Drug Administration's (FDA) accelerated approval guidance, developed initially in response to public demand to speed HIV treatments, permits this evaluation strategy for serious and life-threatening diseases, such as Alzheimer disease.<sup>4</sup> After approval, the expectation is that evidence will be gathered to establish meaningful clinical benefit.<sup>3</sup> The national Alzheimer disease plan lacks a strategy to decide what this evidence is and how it should be gathered and interpreted.

A strategy for gathering and interpreting information is needed before the FDA approves a new drug to prevent Alzheimer disease. After approval, the drug will be marketed under a brand name, and public and private interests and resources will begin to diverge. Recent controversies over the cost of oncology medications show how private interests shape the evidence that establishes that a medication has meaningful clinical benefit, and therefore its price.<sup>5</sup>

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The Anti-Amyloid Treatment in Asymptomatic Alzheimer Study (A4 Study; NCT02008357) offers a case study. The A4 Study is testing whether 3 years of treatment with solanezumab, a drug designed to decrease brain amyloid deposition and which is also being studied in persons with mild-stage Alzheimer disease dementia, slows the rate of cognitive decline in cognitively normal adults ages 65 to 85 years who have evidence of elevated brain amyloid by positron emission tomography scanning. The primary end point of the A4 Study is the Alzheimer Disease Cooperative Study–Preclinical Alzheimer Cognitive Composite (ADCS–PACC), a composite of 4 cognitive tests (2 measures of memory, a measure of executive function, and the Mini-Mental State Exam [MMSE]). What if the trial shows that, compared with placebo, persons on the study drug have slower cognitive decline? How is it established that this is a meaningful clinical benefit? At present, it is not known whether a statistically significant difference in ADCS-PACC scores between patients in different study groups would translate to a clinically meaningful improvement in current or future ability to perform important cognitive tasks, such as managing finances or taking medications.

Among chronic diseases of aging, Alzheimer disease is unique. About three-quarters of the economic effect is related to the need for long-term daily care.<sup>6</sup> Therefore, the benefit of a prevention therapy is shown if it allows people to remain independent (ie, not demented) longer than if they did not take the treatment. Studies should track functional outcomes such as the need for care (either as supervision or assistance) from family or professionals at home or in a long-term care facility.

Answers to 3 questions will help to quantify these outcomes: (1) Is there a slowing of the trajectory of cognitive decline after the onset of dementia? (2) Does treatment lead to a lengthening of the mild or severe stages of dementia? (3) Does treatment delay death and, if so, is treatment associated with compression or expansion of the time living with dementia?

A trial that measures 36 months of treatment cannot answer these questions because the outcomes that establish the efficacy of a drug for preventing Alzheimer disease—maintenance of independent function and decreased caregiving requirements—may not become apparent for considerably more than 3 years. Decision analytic models for the ADCS-PACC outcome can be used to extrapolate effects on other outcomes in the treated group vs the untreated group.<sup>7</sup> Such models can provide estimates of long-term treatment benefits under different assumptions about how the intermediate clinical end point relates to clinical outcomes. Decision analytic models are not a substitute for clinical outcomes, however.

The participants in Alzheimer disease prevention trials should continue to be followed in observational cohort studies. Tracking functional outcomes (for example, managing finances, medications, and driving), as well as scores on cognitive tests, should make it easier to determine whether presymptomatic treatments actually prevent disability and dementia. It is also important to study the relationships between cognitive and clinical outcomes in patients who are more representative than those in clinical trials. This might be possible by adding the cognitive measures used in prevention trials to existing longitudinal

cohorts, such as the Medicare Current Beneficiary Survey, the Framingham Heart Study, the Health and Retirement Study, and the National Health and Aging Trends Study.

The national strategy to establish the benefits of a treatment to prevent Alzheimer disease should address 4 considerations. First, the claim that such a treatment provides clinically meaningful benefit will engage competing interests: the interest of the public—patients, families, and public programs such as Medicare—who want efficacious and affordable treatments and private, for-profit interests of companies who own treatments and understandably also want to maximize the return on their investments. The National Alzheimer Project Act provides a public forum to assemble these interests, prespecify approaches to interpret and weigh evidence, and to make data and data analyses publicly available.

Second, older adults who receive therapies to prevent Alzheimer disease will typically have chronic diseases (eg, cardiovascular disease) that increase their risk of both cognitive decline and death. A treatment-related delay in the onset of dementia should occur before an individual is likely to die from another cause. Balancing the benefits and risks of preventing dementia should include consideration of the competing risk of death from other causes.

Third, persons with Alzheimer disease are said to die twice, first in mind and then in body years later. The judgment that a treatment is valuable because patients lived longer should align with other values such as whether autonomy and quality of life are preserved. For Alzheimer disease, patient-reported measures of autonomy and quality of life are problematic. Even at the mild cognitive impairment stage, patients often underreport the severity of functional losses.<sup>8</sup> Information from spouses or adult children may be unavailable or of uncertain accuracy. Automated monitoring of financial tasks or driving might detect the earliest symptoms, but software that monitors, aggregates, and analyzes financial transactions or driving behaviors raises concerns about intrusions into privacy and independence and also setting validated thresholds that justify intervention.

Fourth, patients may discontinue the medication. If discontinuation rates of Alzheimer prevention drugs are the same as for cardiovascular drugs (5% to 10% per year), the treatment benefit, if there is one, is likely to decrease over time.<sup>9</sup> The discontinuation rates for investigational agents are not yet known; however, if they are to prevent the onset of symptoms, they may need to be taken on a regular basis for years.

Symptomatic Alzheimer disease is common, debilitating, and costly. Although a national plan to prevent symptomatic disease can address these problems, the plan needs an additional strategy to show that expedited approval of new medications will truly improve the lives of the millions of patients with asymptomatic Alzheimer disease who may take them.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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