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GUEST EDITORIAL

Real-world implications of the prospects for prevention of clinical Alzheimer's dementia

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On Valentine's Day 2024, *The Los Angeles Times* published a story entitled, "Inside the plan to diagnose Alzheimer's in people with no memory problems—and who stands to benefit" (1). The story focuses on the financial implications for drug companies and patient advocates. The National Institute on Aging's AHEAD345[1] study (2) is a legitimate, federally funded, randomized clinical trial that is designed to the highest clinical research standards. This is a proven method for new drugs to be put to the most rigorous test using a placebo-controlled, double-blind, state-of-the-art design. The AHEAD345 trial will test the possibility that clinical Alzheimer's dementia may be preventable if diagnosis and intervention are triggered by blood-based biomarker changes detected at midlife despite an absence of symptoms. There is now clear evidence that Alzheimer's pathology develops 20 or more years prior to the appearance of clinical symptoms. The *Times* piece emphasizes that the effort to seize upon this potential window for intervention is at least partially motivated by the prospect that drug companies and dementia advocacy groups will be financially enriched if trials like AHEAD345 succeed. The *Times* article avoids words like "breakthrough" and "moonshot" that are frequently used to describe the mitigation or elimination of major illnesses such as cancer, diabetes, heart disease, and AIDS.

The cost of bringing each new prescription drug to market is estimated at $350 million (3). Usually, generating profits to underwrite ongoing research has been accepted as a sound business model and viewed as evidence of the entrepreneurial spirit of scientists and clinicians. Why was the development of blockbuster drugs that prevent clinical manifestations of atherosclerosis welcomed, while the prospect of preventing dementia is viewed in the first analysis as primarily profit-driven? Is the suffering of younger persons with atherosclerosis and cancer more important than the suffering of elder persons living with dementia and their families? Are scientific discovery and financial profitability mutually exclusive? I would have predicted that any tension between these two outcomes would be a small price to pay if we eliminate an illness that costs 2 trillion dollars per year in the US alone (4).

Many breakthroughs enrich inventors. The Nobel Prize has a monetary value of 11 million Swedish kronor (5). Rigorous trials of drugs are essential, regardless of who stands to benefit either financially or emotionally. While it is entirely reasonable that skeptics hold inventors' feet to the fire, the inventors should be entirely open to scrutiny to realize the common goal of authentic, valid, reproducible data. Skepticism about the outcome does not mean that audacious and potentially lucrative hypotheses should not be tested. The unpredictability of science is the essence of why experiments are conducted.

One goal of the RAND Corporation is to elucidate how successful dementia treatment and prevention might modify the clinical and economic landscape in a range of situations (6). RAND recognizes the substantial variation in the capacities of various healthcare systems to detect, diagnose, and treat or prevent early-stage Alzheimer's with disease-modifying treatments (DMTs). The estimated wait times and the number of patients treated are sensitive to the uptake of brief cognitive assessments by the public and by primary care providers. The estimated average wait times vary by state and can be three times longer in rural areas than in urban areas. Care models that enable primary care physicians to diagnose and evaluate patients for treatment eligibility would significantly reduce wait times for specialists and increase the number of people treated from 2025 through 2044. Improved triage of patients using blood-based biomarker tests could further reduce caseloads for specialists. Widespread delivery of Alzheimer's DMTs will require a combination of strategies to (1) communicate the value of detection and treatment to patients, (2) integrate primary care physicians into the detection and diagnosis pathway, and (3) address capacity disparities across the United States and around the world. These challenges for implementation can only be afforded if DMTs generate enough resources to offset this increase in demand. Critics with legitimate concerns should allow for the possibility that the potential profitability of breakthroughs does not mean that we should avoid asking whether prevention is possible.

Thorny questions remain to be answered. Trials have not been adequately inclusive and diverse (7). Standards for minimum clinically significant benefit are still under development, both for persons living with dementia and for their caregivers (8). Nevertheless, there is no reason not to begin sorting through these implications so that we are appropriately prepared if Alzheimer's prevention succeeds. Current evidence suggests that as many as 76% of patients receiving subcutaneous lecanemab (vs 55% of patients receiving placebo) have a complete arrest of their cognitive decline (9). On what planet is this a bad outcome?

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Competing Interests

Dr. Gandy is a co-founder of Recuerdo Pharmaceuticals. He has served as a consultant in the past for J&J, Diagenic, and Pfizer, and he currently consults for Cognito Therapeutics, GLG Group, SVB Securities, Guidepoint, Third Bridge, MEDACORP, Altpep, Vigil Neurosciences, and Eisai. He has received research support in the past from Warner-Lambert, Pfizer, Baxter, and Avid. He currently receives research support from the NIH and the Cure Alzheimer's Fund.

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[1]Acronym for an NIH clinical trial of blood-based biomarker guided treatment with anti-amyloid antibody or placebo.

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