See article beginning on page 652.

Editor's note: *In this commentary, Drs Reiman, Langbaum, and Tariot comment on an article that was submitted by their own group. They place the article in the context of the Alzheimer's Prevention Initiative, an ambitious research program that they and their colleagues have established with support from the National Institutes of Health, philanthropy, and industry partners.*

Endpoints in Preclinical Alzheimer's Disease Trials

Eric M. Reiman, MD; Jessica B. Langbaum, PhD; and Pierre N. Tariot, MD

Researchers, pharmaceutical companies, funders, regulators, and other stakeholders in the scientific fight against Alzheimer's disease have expressed great interest in the evaluation of putative "preclinical Alzheimer's disease treatments," interventions that are initiated in cognitively unimpaired persons and intended to postpone, reduce the risk of, or completely prevent progression to the clinical stages of Alzheimer's disease. Thank goodness. With the growing number of persons living to older ages, preclinical Alzheimer's disease treatments are urgently needed to avert a catastrophic public health problem, and at least some of the proposed treatments may need to be initiated before the mild cognitive impairment (MCI) or dementia stages of Alzheimer's disease, when the pathology is already extensive, to be most efficacious.

The field is in need of both the scientific means and financial incentives to rapidly evaluate putative preclinical treatments in cognitively unimpaired persons at risk for Alzheimer's disease. The trial endpoints need to help reduce the number of research participants and the time it takes to evaluate putative preclinical Alzheimer's disease treatments, for the world cannot afford to await the results of one large, expensive, and time-consuming trial at a time, and sponsors are unlikely to provide investigational drugs or much support for preclinical Alzheimer's disease trials that last longer than the drug's patent life. What's more, the endpoints must be sufficiently compelling to regulators, such that the effects of an investigational drug on the endpoint could lead to marketing approval. Under standard regulatory agency provisions, the treatment must have "clinically meaningful" effects, including evidence that it impacts relevant cognitive features of Alzheimer's disease and the ability to function (eg, activities of daily living). An impact on functional performance is a high bar for a preclinical Alzheimer's disease trial to reach. Fortunately, regulatory agencies also have accelerated approval provisions for certain treatments, including those for Alzheimer's disease. Under these provisions, it is possible to first approve a treatment if its effects on the primary endpoint are "reasonably likely" to predict a clinically meaningful benefit and then acquire the postmarketing data needed to support a clinically meaningful effect. With those criteria in mind, the search is on for efficient preclinical trial endpoints with sufficient "theragnostic value" in preclinical Alzheimer's disease trials, such that the effects of a treatment on the endpoints are at least reasonably likely to predict a clinical benefit.

In the Alzheimer's Prevention Initiative (API), we and our colleagues have been interested in finding a suitable primary endpoint for potentially license-enabling preclinical Alzheimer's disease trials in cognitively unimpaired persons who, on the basis of their genetic background and age, are at the highest imminent risk for progression to the clinical stages of Alzheimer's disease.[1,2] Utilizing a strategy first proposed by Dr Suzanne B. Hendrix,[3] Dr Langbaum and our colleagues initially used a longitudinal data set from the Rush University Alzheimer's Disease Center to exhaustively search for the combination of cognitive test scores with the greatest power to track cognitive decline in unimpaired older adults who subsequently progressed to the clinical stages of Alzheimer's disease, while controlling for practice and aging effects in other persons who remained cognitively unimpaired over the same time frame. A combination of 7 test scores was found to provide the best power to track the cognitive decline associated with preclinical Alzheimer's disease—although the results depended in part on the studied test battery, and other combinations proved to be almost as good.[4]

How could a composite cognitive test score have better power to track preclinical Alzheimer's disease than the most sensitive individual test in the composite? By capturing an additional aspect of preclinical Alzheimer's disease decline and not adding to measurement noise. Because it is difficult to know how well any tests might do in that regard, we have made the case for the use of empirically generated and independently confirmed composite cognitive test scores in the preclinical tracking of Alzheimer's disease and the evaluation of preclinical Alzheimer's disease treatments.

In this issue of *JCP*, our group describes the effort to characterize the composite cognitive test score that was selected for the evaluation of an investigational amyloid-β modifying treatment in the API autosomal dominant Alzheimer's disease (ADAD) trial.[5] The analysis capitalized on longitudinal data acquired by Francisco Lopera and colleagues in *PSEN1* E280A mutation carriers and noncarriers from the world's largest ADAD kindred in Antioquia, Colombia. Data from initially unimpaired *PSEN1* E280A mutation carriers at least 30 years of age were used to provide an indicator of preclinical Alzheimer's disease decline, and data from the noncarriers in that age group were used to control for practice and aging effects. Despite differences in language, test batteries, frequency of follow-up assessments, and application to a younger cohort, the analysis found that a roughly similar combination of cognitive test scores had the best power to track preclinical ADAD decline. This analysis permitted us to estimate the number of mutation carriers needed for our 5-year preclinical ADAD trial, now in progress, using the API composite cognitive test score as the primary endpoint (ClinicalTrials.gov identifier NCT01998841).

Thanks to the generosity of several research groups, we have begun to extend our findings to a growing number of longitudinal cohorts and to prepare for the use of a similar

Submitted: *May 5, 2014; accepted May 5, 2014.*

Corresponding author: *Eric M. Reiman, MD, Banner Alzheimer's Institute, 901 E Willetta St, Phoenix, AZ 85006 (eric.reiman@bannerhealth.com).*

J Clin Psychiatry 2014;75(6):661–662 (doi:10.4088/JCP.14com09235).

composite cognitive test score in the API apolipoprotein E (*APOE*) ε4 preclinical Alzheimer's disease trial, which is planned in cognitively unimpaired *APOE* ε4 homozygotes, 60–75 years of age, who have a particularly high imminent risk of progression to the clinical stages of late-onset Alzheimer's disease. Looking ahead, we anticipate that different composite cognitive test scores will be used in preclinical Alzheimer's disease trials, depending in part on the longitudinal data needed to characterize the optimal test combination and statistical power in the at-risk group being considered for study. Some groups have expressed interest in using computational test batteries or more difficult cognitive tests to further optimize the power to track preclinical Alzheimer's disease decline, again depending in part on the longitudinal data needed to demonstrate their added value in the relevant at-risk population. Others are using alternate endpoints, such as frequency of or time to progression to MCI or dementia, whichever comes first. At the present time, it seems prudent for preclinical Alzheimer's disease trials to continue to have flexibility in the selection of the most appropriate endpoint. At the same time, it also seems prudent for the different trials to acquire the data necessary to compare findings across trials. What about using brain imaging or other biological measurements as endpoints in preclinical Alzheimer's disease trials? While such measures do have the potential to track Alzheimer's disease and evaluate preclinical treatments with improved statistical power, they are not yet ready to serve as primary endpoints in license-enabling trials. Additional data from preclinical Alzheimer's disease trials themselves are needed to investigate the extent to which a preclinical treatment moves different biomarkers, to determine whether it does so in a way that is free from a potentially confounding effect unrelated to disease-slowing, and, most importantly, to establish the relationship between the treatment's biomarker and clinical effects. For this reason, the API trials are specifically designed to embed the most promising biomarkers in the trials and relate a treatment's 2-year biomarker effects to its 5-year effects on the composite cognitive test score.

The advancement of endpoints for preclinical Alzheimer's disease trials has benefited greatly from several factors: the clarity, consistency, and flexibility that the US Food and Drug Administration (FDA) has shown in its public comments and draft guidance statement on the use of endpoints in early clinical and preclinical Alzheimer's disease trials[6]; similar public comments from the European Medicines Agency; progress in the design of several other preclinical Alzheimer's disease trials, including the Alzheimer's Disease Cooperative Study (ADCS) A4 Trial,[7] Dominantly Inherited Alzheimer's Network Therapeutic Unit (DIAN-TU) Trial,[8–11] and TOMMORROW trial[12,13]; the growing interest of drug sponsors in preclinical AD trials; and the interest of public and private funders in the development of theragnostic biomarker endpoints, as reflected by the Accelerating Medicines Partnership, in which National Institutes of Health and industry funds will be used to include additional exploratory biomarker endpoints in 3 of the publicly supported preclinical Alzheimer's disease trials. In an effort to work together on the issue of preclinical Alzheimer's disease trial endpoints and other issues, the Collaboration for Alzheimer's Prevention was formed by leaders from the ADCS A4 Trial, API, DIAN-TU, Alzheimer's Association, Fidelity Biosciences Research Initiative, National Institute on Aging, and FDA.

When it comes to the optimization suitability of endpoints in preclinical Alzheimer's disease trials, there is much more to do and learn. But the recent momentum has been awfully encouraging.

Author affiliations: Banner Alzheimer's Institute and Banner Research (all authors), University of Arizona College of Medicine (Drs Reiman and Tariot), Translational Genomics Research Institute (Dr Reiman), and Arizona Alzheimer's Consortium (all authors), Phoenix.
Potential conflicts of interest: **Dr Reiman** has been a consultant for Chiesi. **Dr Tariot** has received consulting fees from Abbott, AbbVie, AC Immune, Boehringer-Ingelheim, California Pacific Medical Center, Chase Pharmaceuticals, CME Inc, Medavante, Otsuka, and Sanofi-Aventis; has received consulting fees and research support from AstraZeneca, Avanir, Bristol-Myers Squibb, Cognoptix, Janssen, Merck, and Roche; has received research support from Baxter, Functional Neuromodulation, GE, Genentech, Pfizer, Targacept, National Institute on Aging, and Arizona Department of Health Services; holds stock options in Adamas; and is listed as a contributor to a patent owned by the University of Rochester, Biomarkers of Alzheimer's Disease. **Dr Langbaum** reports no potential conflict of interest.
Funding/support: This work is supported by National Institute on Aging grants RF1 AG041705 (Drs Reiman and Tariot), UF1 AG046150 (Drs Reiman and Tariot), R01 AG031581 (Dr Reiman), P30 AG19610 (Dr Reiman), Genentech, Avid Radiopharmaceuticals, Banner Alzheimer's Foundation, Anonymous Foundation, Nomis Foundation, Arizona Alzheimer's Consortium, and the State of Arizona.
Disclaimer: Dr Reiman, Deputy Editor of *JCP* and Section Editor of the Focus on Alzheimer's Disease and Related Disorders section, and Dr Tariot, *JCP* editorial board member, were not involved in the editorial evaluation or decision to publish this commentary.

REFERENCES

1. Reiman EM, Langbaum JBS, Tariot PN. Alzheimer's Prevention Initiative: a proposal to evaluate presymptomatic treatments as quickly as possible. *Biomarkers Med*. 2010;4(1):3–14.
2. Reiman EM, Langbaum JB, Fleisher AS, et al. Alzheimer's Prevention Initiative: a plan to accelerate the evaluation of presymptomatic treatments. *J Alzheimers Dis*. 2011;26(suppl 3):321–329.
3. Hendrix SB. Measuring clinical progression in MCI and pre-MCI populations: enrichment and optimizing clinical outcomes over time. *Alzheimers Res Ther*. 2012;4(4):24.
4. Langbaum JB, Hendrix SB, Ayutyanont N, et al. An empirically derived composite cognitive test score with improved power to track and evaluate treatments for preclinical Alzheimer's disease [published online ahead of print April 18, 2014]. *Alzheimers Dement*.
5. Ayutyanont N, Langbaum JBS, Hendrix SB, et al. The Alzheimer's Prevention Initiative composite cognitive test score: sample size estimates for the evaluation of preclinical Alzheimer's disease treatments in presenilin 1 E280A mutation carriers. *J Clin Psychiatry*. 2014;75(6):652–660.
6. Food and Drug Administration. Guidance for industry Alzheimer's disease: developing drugs for the treatment of early stage disease. Draft guidance. 2013. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338287.pdf. Updated February 2013. Accessed May 6, 2014.
7. Sperling RA, Rentz DM, Johnson KA, et al. The A4 study: stopping AD before symptoms begin? *Sci Transl Med*. 2014;6(228):228fs13.
8. Bateman RJ, Xiong C, Benzinger TL, et al; Dominantly Inherited Alzheimer Network. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med*. 2012;367(9):795–804.
9. Morris JC, Aisen PS, Bateman RJ, et al. Developing an international network for Alzheimer research: the Dominantly Inherited Alzheimer Network. *Clin Investig (Lond)*. 2012;2(10):975–984.
10. Mills SM, Mallmann J, Santacruz AM, et al. Preclinical trials in autosomal dominant AD: implementation of the DIAN-TU trial. *Rev Neurol (Paris)*. 2013;169(10):737–743.
11. Moulder KL, Snider BJ, Mills SL, et al. Dominantly Inherited Alzheimer Network: facilitating research and clinical trials. *Alzheimers Res Ther*. 2013;5(5):48.
12. Roses AD, Saunders AM, Lutz MW, et al. New applications of disease genetics and pharmacogenetics to drug development. *Curr Opin Pharmacol*. 2014;14:81–89.
13. Crenshaw DG, Gottschalk WK, Lutz MW, et al. Using genetics to enable studies on the prevention of Alzheimer's disease. *Clin Pharmacol Ther*. 2013;93(2):177–185.