

# Use of Alzheimer Disease Biomarkers Potentially Yes for Clinical Trials but Not Yet for Clinical Practice

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**R**ESearch in ALZHEIMER DISEASE (AD) IS RAPIDLY MOVING toward the point of the earliest possible identification of the underlying disease processes. These include the accumulation of A $\beta$  plaques, tau tangles, and neuron as well as synaptic loss, and it is likely that these do not all occur contemporaneously. Many investigators contend that, by the time the clinical symptoms appear, sufficient AD pathology and neurodegeneration have occurred, which if irreversible, may reduce the efficacy of disease-modifying therapy for clinically manifest AD.<sup>1</sup> As such, efforts are under way to try to identify the onset of these pathological processes that culminate in clinically manifest AD dementia. However, to accomplish this, the underlying pathology must be detected, possibly through the use of neuroimaging and chemical biomarker measures. In this issue of JAMA, Mattsson and colleagues<sup>2</sup> report their evaluation of the utility of cerebrospinal fluid (CSF) markers for AD in a large multicenter study.

The investigators from the Swedish Brainpower CSF Initiative enrolled individuals with mild cognitive impairment (MCI) from 12 centers in Europe as well as healthy individuals as controls and those with mild AD for comparison. They identified 750 individuals as having MCI and followed them for at least 2 years to determine whether the CSF profile at baseline of A $\beta$ 42, total tau (T-tau), and phosphorylated tau (P-tau) predicted the ultimate clinical course. They found that CSF A $\beta$ 42, T-tau, and P-tau could be used to predict outcomes and thus suggest that these markers may be useful in identifying patients for clinical trials and possibly screening tests in memory clinics.

This group of investigators has been studying these issues for several years, and their study represents a tour de force of clinical and laboratory data collections. However, their study also represents several key challenges that need to be addressed before CSF markers are ready for broad clinical applications, although these markers already are being used in clinical trials of disease-modifying therapies for AD.

Mild cognitive impairment is a heterogeneous condition, and based on the underlying conceptual nature of the condition, this is to be expected.<sup>3,4</sup> International consensus meetings have characterized the construct by subtypes into amnesic and non-amnesic MCI<sup>5,6</sup> in an attempt to explain some of the heterogeneity. Amnesic MCI of a presumed degenerative etiology is generally considered to be the forerunner of clinical AD, and

Mattsson et al<sup>2</sup> have diagnosed MCI with that presumption. However, the investigators combined clinical data from 12 different memory disorders centers, using different instruments and likely different implementation of the criteria and consequently may have assembled a group of individuals with significant clinical variability. As such, while they present the Mini-Mental State Examination scores and demographic data, without the presentation of the other clinical data a precise comparison of the individuals from the different centers is difficult. The investigators describe that they enrolled a consecutive series of individuals presenting to memory centers with symptoms leading to the diagnoses of MCI or AD. Despite this variability, the investigators reported an annual rate of progression to AD of 11%, which is typical for referral center cohorts.<sup>7</sup>

Similarly, there was likely considerable variability with respect to the CSF collection and assays, and the authors clearly acknowledge that their CSF assays require further standardization. The coefficients of variation from other sites were discrepant from the primary site, and a formula was used to “correct” these data. This may have made the results comparable in a statistical sense from the various sites; however, it is also likely that the significant variability in the laboratory data could have compounded the problems with the clinical variability. The investigators in this report are accomplished in AD biomarker research and aware of the hurdles that need to be surmounted to bring an AD biomarker from the initial discovery stage to a validated test for AD diagnosis.<sup>8</sup>

Despite these potential sources of variability, the study documented the utility of CSF biomarkers to predict, with good accuracy, the outcome of individuals with MCI. Moreover, with further mining of their data, Mattsson et al may improve on their CSF biomarker algorithm. Shaw et al<sup>9</sup> recently reported that APOE genotype contributed incrementally to test accuracy when combined with measures of CSF A $\beta$  and tau. Thus, the study by Mattsson et al is an important contribution toward the goal of developing disease-modifying therapies based on the use of biomarkers and clinical measures.

Despite the considerable clinical and laboratory variability, the results appear plausible and enticing. As the authors indicate, this multicenter study replicated the results of smaller single-center studies, with the caveat that some of the prior study samples were included in this study. The data likely reflect the underlying pathological processes of AD in some in-

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dividuals with MCI; however, it is premature to recommend application of these techniques in clinical practice. The inherent clinical and laboratory variability precludes the adoption of these measures at this time. Significant refinement of the assay procedures is necessary before these techniques can be recommended for general clinical use along the lines described in previous publications.<sup>8,9</sup>

An effort in this direction is now under way in North America known as Alzheimer Disease Neuroimaging Initiative (ADNI)<sup>9,10</sup> and is complemented by similar studies in Europe, Japan, and Australia. This study represents 57 centers in the United States and Canada and was designed to evaluate the utility of neuroimaging and clinical biomarkers in characterizing the course of amnesic MCI with the intention of predicting clinical AD before the full criteria for dementia are met. A major focus of this study also involves reducing variability in the clinical, neuroimaging, and laboratory procedures, including refining the clinical criteria for amnesic MCI (it is noteworthy that the clinical cohort recruited in ADNI has identical clinical features and rates of progression to AD as seen in an earlier clinical trial on amnesic MCI<sup>11</sup>); standardizing neuroimaging procedures for magnetic resonance imaging, fluorodeoxyglucose positron emission tomography (PET), and PiB (Pittsburgh Compound B) PET; and centralizing the laboratory analysis of CSF biomarkers to ensure consistency and reliability. The biomarker data will be integrated with imaging and clinical data with the goal of identifying the optimal panel to use for predictive testing for AD, AD diagnosis, and clinical trial monitoring.

Of critical importance, however, is what the clinician and patient will do with such results. The sensitivity and specificity of A $\beta$ 42, T-tau, and P-tau in the study by Mattsson et al were sufficient to be used for screening but not as a diagnostic test. Alzheimer disease has no treatment to prevent or alter the course of the disease, so making the diagnosis with good accuracy may aid in planning but also could be devastating news for some patients and families. Furthermore, false positives and false negatives occur as with any screening test. However, as biomarkers

become more sophisticated, they are likely to take on an increasingly important role in the diagnosis and management of AD.

The study by Mattsson et al<sup>2</sup> represents a major step forward in suggesting that biomarkers may have sufficient accuracy to be used in the AD prodromal phase. The report highlights the challenges but also suggests solutions. Subsequent prospective investigations should clarify the true utility of these measures.

**Financial Disclosures:** Dr Petersen reported serving as chair of the safety monitoring committee and as a consultant for Elan Pharmaceuticals; as chair of the data monitoring committee for Wyeth Pharmaceuticals; and as a consultant for GE Healthcare. Dr Trojanowski reported no disclosures.

**Funding/Support:** This work was supported through Alzheimer's Disease Neuroimaging Initiative grant U01 AG24904.

**Role of the Sponsor:** The Alzheimer's Disease Neuroimaging Initiative had no role in the preparation or approval of this editorial.

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## Lifestyle and Cardiovascular Health Individual and Societal Choices

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**A**S PART OF THE EPIDEMIOLOGIC TRANSITION INTO THE 21st century, chronic diseases—specifically, cardiovascular diseases—have become the leading cause of death and disability in most countries in the world.<sup>1</sup> Hence, clinical and public health interventions must aim at reducing the burden of cardiovascular disease

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in populations. Secular trends in cardiovascular disease morbidity and mortality indicate that some progress has been made, and cardiovascular mortality has decreased. However, the incidence of cardiovascular disease has remained largely stable over the past 2 decades, which, given the decrease in cardiovascular mortality, suggests that medical care

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