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# Revolutionizing Alzheimer's disease and clinical trials through biomarkers

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**Abstract** The Alzheimer's Association's Research Roundtable met in May 2014 to explore recent progress in developing biomarkers to improve understanding of disease pathogenesis and expedite drug development. Although existing biomarkers have proved extremely useful for enrichment of subjects in clinical trials, there is a clear need to develop novel biomarkers that are minimally invasive and that more broadly characterize underlying pathogenic mechanisms, including neurodegeneration, neuroinflammation, and synaptic dysfunction. These may include blood-based assays and new neuropsychological testing protocols, as well as novel ligands for positron emission tomography imaging, and advanced magnetic resonance imaging methodologies. In addition, there is a need for biomarkers that can serve as theragnostic markers of response to treatment. Standardization remains a challenge, although international consortia have made substantial progress in this area and provide lessons for future standardization efforts.



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## 1. Introduction

A biomarker is a characteristic that can be objectively measured and evaluated as an indicator of a normal or pathologic process, or as a measure of response to therapy [1] (Biomarker Working Group 2001). Biomarker research has revolutionized the understanding of Alzheimer's disease (AD) and is in the process of transforming the design of AD clinical trials. Until recently, AD was only imprecisely diagnosed in life using clinical assessments during the dementia stage or at time of death by neuropathology. Nonetheless, substantial progress over the past decades in

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developing cerebrospinal fluid (CSF) and imaging biomarkers has shown that AD brain changes can be detected and used for diagnosis and prognosis of AD [2,3].

As these biomarkers have been included in observational studies of AD, better understanding of the biochemical and pathologic changes of AD has occurred. This has led to confirmation of the hypothesis [4,5] that AD is a disease progressing from preclinical to early and then late clinical stages, and which is now emphasized in novel research diagnostic criteria incorporating biomarkers [6]. Previously, drug developers focused on the dementia stage of the disease. This has now radically changed as clinical trials move toward earlier stages of AD, before extensive neurodegeneration has occurred [7–9], and even to secondary prevention before symptom onset [10–12], when disease-modifying treatments are likely to have maximal effect. Biomarkers play a key role in the design of these trials, both for inclusion of subjects with AD pathology and to track biological effects of drugs. Yet even though it is a widely held belief that AD biomarkers can be used for diagnosis, prognosis/prediction, and to monitor the effects of therapy [1,13], in the absence of an effective treatment to slow progression of AD (and the underlying pathogenic processes), the link between biomarkers and effect on disease cannot be established.

Data from many studies all over the world, including the Alzheimer's Disease Neuroimaging Initiative [14], its worldwide partners (WW-ADNI) [15], and the Dominantly Inherited Alzheimer's Network (DIAN) [16], have done much to delineate the temporal changes in biomarkers over time and clarify their relationship to cognition and function. Yet despite the field's growing acceptance of the need for biomarkers in drug development, the belief that biomarkers could improve clinical trial design and the success of those trials was shaken by recent mixed clinical trial results. The phase III bapineuzumab trial, in particular, went forward in part based on findings in phase II studies that showed modest reductions in brain amyloid [17], and CSF phosphorylated tau (P-tau) concentrations [18]. The presumption that these biomarker effects represented a clinically relevant treatment effect, however, was called into question when no clinical benefit was found in the phase III trials, despite hints that biomarkers were impacted by therapy [19]. The phase III results for solanezumab also did not provide statistically significant effects for coprimary outcomes; however, planned secondary analyses were consistent with clinical benefit of solanezumab in patients with mild AD dementia without evidence of an impact of solanezumab on brain amyloid burden, downstream neurodegeneration markers of CSF tau proteins or brain volume, but with an increase in total CSF $A\beta_{42}$ and $A\beta_{40}$ [20].

In this setting, the Alzheimer's Association Research Roundtable convened a meeting in May, 2014 to explore the extent to which biomarkers have furthered our understanding of the disease, supported drug development, and improved the care of patients; and more importantly, to identify what needs to be done to realize their full potential. Can biomarkers indeed provide answers to guide future trials toward more successful outcomes? The Roundtable examined evidence to support this premise, identified unanswered questions, and explored areas of potential collaboration in precompetitive space among key stakeholders that might expedite this effort.

## 2. Biomarkers as enrichment tools for clinical trials

Further critical examination of the bapineuzumab and solanezumab studies suggested several possible reasons for the negative trial results. One contributing factor is that some of the enrolled trial subjects may not have AD [21]. Clinical criteria for patient inclusion in each program resulted in study populations with a significant percentage of participants without evidence of brain amyloid by positron emission tomography (PET; ~7 and 36% amyloid negative in apolipoprotein E (*APOE*) ε4 carriers and noncarriers, respectively) [22]. Using amyloid biomarkers to enrich for trial subjects who are amyloid-positive—and thus presumably on the AD trajectory—may improve the ability of future trials to detect a treatment effect especially for anti-amyloid therapies. Indeed, data from several studies have shown that among cognitively normal elderly, those who are amyloid-positive are at greater risk of decline compared with those who are amyloid-negative [6,23–26]. In the placebo arms of both the bapineuzumab and solanezumab studies, which enrolled subjects with mild-to-moderate AD, amyloid-positive subjects had significant decline on both cognitive and functional measures, whereas the amyloid-negative subjects did not [22]. Importantly, the effect of amyloid pathology on longitudinal memory decline may be greater in *APOE* ε4 carriers compared with *APOE* ε4-noncarriers [27].

Disease severity may be another factor that contributed to the negative trial results. In comparison with subjects with mild disease, those with more advanced clinical disease may have far more advanced neurodegeneration. The modest impact of treatment on the underlying pathology and markers of the pathology may not be sufficient to translate to a clinical benefit. In the bapineuzumab studies, even individuals with the largest reported decrease in amyloid still had elevated values in the AD range and although significant treatment differences were observed between bapineuzumab and placebo, the change from baseline values in the bapineuzumab groups ranged ~0%–10% (with reductions in the CSF P-tau concentration and inhibited further accumulation of brain amyloid by PET) [17–19]. Finally, it is possible that the presence of copathologies (for example tau, vascular, Lewy body, or transactive response DNA binding protein 43 [TDP-43] pathology) may influence cognitive trajectories independent of amyloid pathology [28,29] and impact trial results.

Many trials currently underway or planned are therefore enrolling subjects in earlier stages of disease and using amyloid biomarkers, either amyloid PET imaging or CSF $A\beta_{42}$ levels, to enrich for trial subjects thought more likely to