

## **Advances in Biomarkers and Modeling for the Development of Improved Therapeutics: Early Alzheimer's Treatment**

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Alzheimer's disease (AD) is a gradually progressive neurodegenerative condition, and substantial evidence suggests that the pathologic process begins years and perhaps even decades prior to when a clinical diagnosis of AD can be made using current diagnostic criteria. Biomarkers provide a promising means to determine the presence of AD pathology before a diagnosis of AD can be made using clinical measures alone. Early treatment for AD could be contemplated for patients who have small changes in cognition, but who are not demented; similarly, treatment could be considered for individuals who are cognitively normal, but who have biomarker evidence for underlying AD pathology. Screening of asymptomatic populations for evidence of an underlying disease state has been performed for cardiovascular disease using serum cholesterol, for Huntington's disease using direct gene testing, and for a variety of cancers including breast, colon and prostate. Some aspects of these screening programs may be applicable to future AD screening programs. Clinical trial designs for patients with cognitive decline who are not demented have generally focused on "time to conversion" to AD. Based on published data and data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), use of continuous measures of cognition and of functional abilities is likely to provide more reliable and meaningful data for trials with these individuals. Finally, the design for Phase 2 trials that most reliably predicts efficacy in Phase 3 has not yet been determined for patients with manifest AD, and is even less understood for individuals prior to a diagnosis of AD. The use of biomarkers in Phase 2 trials of patients with little or no cognitive symptoms may provide important information regarding dose selection and probability of success in Phase 3 studies.