

## Barriers for Prevention and Prodromal AD Trials

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**A**s clinical trials for Alzheimer's disease (AD) have shifted, in large part, towards preclinical and prodromal stages of the disease, the need for novel recruitment, randomization, and retention strategies has emerged. Recruitment strategies include national and multi-national registries, such as the European Prevention of Alzheimer's disease (EPAD) and the Global Alzheimer's Platform (GAP) registries that enroll broad, heterogeneous populations from which candidates appropriate for individual trials can be identified; as well as more selective cohorts such as those that enroll individuals with certain risk factors, biomarker findings, or a genetic predisposition to the disease (1). These various registries and cohorts reflect the idiosyncratic nature of the trials for which they are designed, each of which results in different barriers to be overcome.

### Disease progression and prevention

Numerous studies have provided evidence supporting the hypothesis that AD neuropathology develops slowly over time, with the deposition of amyloid in the brain beginning as much as two decades before cognitive impairment (2). Intervening before pathology begins to develop -- primary prevention -- would thus require identifying those individual who are clinically normal but at risk of developing the disease. Once the pathological process has begun, secondary prevention measures would aim to prevent or delay the emergence of symptoms in those with preclinical AD or slow progression of symptoms in those with mild cognitive impairment (prodromal AD). Finally, in those with mild, moderate, or severe impairment, treatments focus on improvement cognition and behavior and slowing progression of the disease.

These disease stages correlate with temporal changes in biomarkers, as proposed by Jack et al in 2010 (3) and later demonstrated in individuals with autosomal dominant forms of AD (4) and in longitudinal observational studies of aging individuals (5), as well as in other research cohorts. In a population-based study published by Jack et al in 2014 (6), cognitively normal subjects were classified into four categories based on biomarkers of amyloid and neurodegeneration in the brain. Amyloid was assessed by PET imaging using Pittsburgh Compound B, while neurodegeneration

was determined by FDG-PET and/or MRI measures of hippocampal volume. The results of this study expanded on the staging system for preclinical AD proposed by the National Institute on Aging-Alzheimer's Association working group (7) and operationalized the research criteria for asymptomatic at-risk for AD proposed by the International Working Group (IWG) in 2014 (8). Importantly, population frequency biomarker curves were further refined based on age, sex, and ApoEε4 status, a genetic marker associated with increased risk of developing AD (9).

### Clinical Trials in the Era of Prevention

This new understanding of how biomarkers can be used to categorize individuals with normal cognition into subgroups based on the presence of pathology in their brains has important implications for investigators and sponsors designing clinical trials. Already, several secondary prevention clinical trials are underway, targeting asymptomatic individuals with genetic predisposition to the disease or positive biomarker studies (NCT01998841, NCT01760005, NCT02008357, NCT02565511), (10-12), as well as symptomatic individuals with mild cognitive impairment or mild AD dementia (NCT01767909, NCT01900665, NCT02477800).

Moving forward, however, it will be essential to test prevention strategies on heterogeneous cohorts that reflect the real-life frequencies of preclinical and prodromal AD. To this end, the registries mentioned earlier will be extremely valuable. In addition, there is a critical need to amplify the patient and caregiver voice in clinical trial efforts. To this end, partnerships have arisen, such as the National Alzheimer's & Dementia Patient & Caregiver-Powered Research Network (AD PCPRN), a collaboration between the Mayo Clinic, the University of Florida, Brain Health Registry and USAgainstAlzheimer's (USA2) with funding from the Patient Centered Outcomes Research Institute (PCORI). The National AD PCPRN aims to enroll an increasingly large number of subjects, especially minority subjects who are underrepresented in existing clinical studies, into a patient-centered network. The Network plans to obtain self-reported information and baseline and longitudinal cognitive testing on participants, test a computable patient phenotype, and screen and refer individuals for potential participation in clinical trials.

The AD PCPRN also intends to create a common dataset for use by all of its partners and fund research that could capture even larger numbers of participants. For example, one project would interrogate electronic health records databases from large healthcare networks to search for those with a particular diagnosis and obtain permission to contact them to suggest enrolling in a clinical trial.

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