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# Preclinical Alzheimer Disease - The Challenges Ahead

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## **Abstract**

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## **Keywords**

aging and dementia, brain imaging, cognitive neurology

## **Disciplines**

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## Preclinical Alzheimer disease —the challenges ahead

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## Abstract

There is growing recognition that the pathophysiological process of Alzheimer disease (AD) begins many years prior to clinically obvious symptoms, and the concept of a presymptomatic or preclinical stage of AD is becoming more widely accepted. Advances in biomarker studies have enabled detection of AD pathology *in vivo* in clinically normal older individuals. The predictive value of these biomarkers at the individual patient level, however, remains to be elucidated. The ultimate goal of identifying individuals in the preclinical stages of AD is to facilitate early intervention to delay and perhaps even prevent emergence of the clinical syndrome. A number of challenges remain to be overcome before this concept can be validated and translated into clinical practice.

## Introduction

Alzheimer disease (AD) remains the only major cause of mortality without an effective disease-modifying treatment. As the population continues to age and the number of clinical trial disappointments increases, both public and scientific communities are recognizing the urgent need to discover these treatments. Many researchers in the field are concerned that the failure of clinical trials is attributable, at least in part, to testing of potential disease-modifying therapeutic agents too late in the pathophysiological course of AD. Thus, a possible strategy to achieve success is earlier intervention.

Data from both genetic at-risk and biomarker at-risk cohorts support implementation of such a strategy. The complex pathophysiological process of AD begins many years before symptoms of the disease emerge. Through use of fluid and imaging biomarkers (Box 1), evidence of AD pathology can now be detected *in vivo* in clinically normal older

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### Competing interests

R. A. Sperling declares associations with the following companies: Avid/Lilly, Bayer, Biogen Idec, Bristol-Myers Squibb, Eisai, Janssen, Merck, Pfizer, Roche, Satori. J. Karlawish declares associations with the following companies/organizations: SeniorBridge, University of Pennsylvania. K. A. Johnson declares associations with the following companies: Avid/Lilly, Bayer, Bristol-Myers Squibb, Elan, General Electric Health Care, Genzyme, Janssen, Pfizer, Siemens. See the article online for full details of the relationships.

individuals. This silent stage of AD—when the disease has begun in the brain but symptoms are not yet clinically evident—has been termed ‘preclinical AD’.<sup>1</sup> Intervention at this stage would offer the opportunity to delay or ultimately even prevent the onset of cognitive impairment and dementia. Translation of this concept into successful detection and treatment for older individuals, however, requires a number of substantial challenges to be overcome. In this article, we discuss the specific issues challenging successful implementation of preclinical criteria in the clinical research setting and, ultimately, incorporation of the concept of preclinical AD into medical practice.

### Box 1

#### Biomarkers of preclinical AD

##### Markers of amyloid- $\beta$ accumulation

- Cerebrospinal fluid amyloid- $\beta_{42}$
- PET amyloid imaging

##### Markers of neurodegeneration or neuronal injury

- Cerebrospinal fluid tau and phosphorylated tau
- Functional imaging:  $^{18}\text{F}$ -fluorodeoxyglucose PET or functional MRI
- Volumetric MRI: measures of hippocampal atrophy and cortical thinning

Abbreviation: AD, Alzheimer disease.

## Defining preclinical AD

Recent guidelines by the US National Institute on Aging and the US Alzheimer’s Association provide a conceptual framework for defining the stages of preclinical AD (Box 2).<sup>1</sup> Stage 1 is characterized by evidence of amyloid- $\beta$  ( $\text{A}\beta$ ) accumulation on PET  $\text{A}\beta$  imaging or cerebrospinal fluid (CSF) assays. Stage 2 involves cerebral amyloidosis plus evidence of neurodegeneration, such as elevated CSF tau levels or abnormalities on functional or structural neuroimaging. Stage 3 is characterized by amyloidosis plus neurodegeneration with evidence of very subtle cognitive decline that does not yet meet the criteria for mild cognitive impairment (MCI). Recent cross-sectional data from the Dominantly Inherited Alzheimer Network (DIAN),<sup>2</sup> as well as longitudinal data from the Alzheimer’s Disease Neuroimaging Initiative<sup>3</sup> and the Mayo Clinic,<sup>4</sup> provide some preliminary support for this model.

### Box 2

#### Proposed staging of preclinical AD

Definitions for the preclinical stages of AD were recently outlined by the US National Institute on Aging:<sup>1</sup>

- Stage 1: Asymptomatic cerebral amyloidosis
- Stage 2: Amyloidosis + evidence of neurodegeneration or neuronal injury
- Stage 3: Amyloidosis + neurodegeneration + evidence of subtle cognitive decline

Two additional categories have since been proposed:<sup>5</sup>

- Stage 0: Older individuals with no biomarker evidence of AD pathology

- Suspected Non-Alzheimer Pathology (SNAP): Individuals showing biomarkers of neurodegeneration without positive markers of amyloid accumulation

Abbreviation: AD, Alzheimer disease.

Whether this staging framework will prove valid remains to be seen, and emerging data suggest a number of issues that deserve further consideration. A recent paper from Jack and colleagues<sup>5</sup> proposed two additional categories: stage 0 to denote individuals who do not show detectable evidence of disease, and a category termed Suspected Non-Alzheimer Pathology (SNAP) that denotes individuals who have biomarker evidence of neurodegeneration in the absence of amyloid-marker positivity. The SNAP group could represent individuals in early stages of other neurodegenerative diseases, particularly as a small subgroup of individuals in this category harbour the  $\epsilon 4$  allele of the apolipoprotein E (*APOE*) gene—a key risk factor for AD.<sup>4,5</sup>

### Defining ‘biomarker positivity’

Designation of a category such as stage 0 is clearly important as it acknowledges that the majority of older individuals do not have evidence of AD pathology. At least a small proportion of individuals who are classified as stage 0, however, are probably experiencing early AD processes that are undetectable with current biomarkers—such as oligomeric forms of  $A\beta$ —and could become positive for  $A\beta$  biomarkers within a few years. For example, several studies of clinically normal young and early-middle-aged individuals who are genetically predisposed to AD—both *APOE*  $\epsilon 4$  homozygotes and presenilin 1 (*PSEN1*) mutation carriers—have demonstrated evidence of functional imaging abnormalities before the typical age of onset of detectable  $A\beta$  deposition.<sup>6,7</sup> These individuals might have synaptic toxicity caused by forms of  $A\beta$  that we cannot measure, or these functional alterations could be due to metabolic vulnerabilities that are independent of  $A\beta$  effects.

Recent longitudinal data suggest that each year, approximately 3% of clinically normal individuals cross the threshold from ‘amyloid-negative’ to ‘amyloid-positive’ on PET imaging.<sup>8</sup> Therefore, in addition to the challenge of translating the criteria for biomarker positivity into clinical practice, current definitions of ‘biomarker-positive’ are likely to change as new methods that enable more-sensitive detection of biomarkers of the earliest alterations in  $A\beta$  metabolism and synaptic function become available. Moreover, longitudinal data will probably continue to alter our definitions of biomarker positivity, similarly to the ongoing revisions of recommended levels for LDLs for prevention of cardiac disease.

Markers of aberrant metabolism and accumulation of  $A\beta$  are currently the first to manifest in the hypothesized sequence of AD biomarkers. This finding might reflect the greater specificity of  $A\beta$  biomarkers compared with biomarkers of neurodegeneration, as these latter markers may indicate non-AD-related processes, including other age-related neurodegenerative diseases and normal ageing. A well-established relationship exists between advancing age and most of the markers of neurodegeneration, such as hippocampal atrophy, even among older individuals who are negative for biomarkers of  $A\beta$ . Thus, it remains to be seen whether individuals who are negative for amyloid markers, but positive for markers of neurodegeneration (that is, the SNAP group), will become positive for amyloid markers over time and demonstrate similar rates of clinical decline towards AD dementia, or whether they will instead progress towards other dementia syndromes. Also of note, markers of  $A\beta$  accumulation can be positive in individuals who have dementia with Lewy bodies and/or cerebral amyloid angiopathy, and are not equivalent to a clinical diagnosis of AD.

The ability to detect amyloid accumulation with either PET imaging or CSF testing has facilitated research in larger cohorts, and probably accounts for some of the recent high level of interest in amyloid biomarkers. In future, specific markers of excitotoxicity, synaptic dysregulation, synapse loss and neuronal loss (including apoptosis) might permit more-precise staging of the evolution of AD pathology, and development of techniques to image markers of some of these processes, such as tau, will probably enable longitudinal studies in larger cohorts.

An additional challenge to establishing the definition of preclinical AD is the possibility that the biomarkers currently in use might not reflect the underlying pathophysiological process of AD. For example, existing biomarkers of amyloid (CSF levels of A $\beta$ <sub>1-42</sub> monomer, and PET amyloid imaging) primarily indicate when A $\beta$  has begun to accumulate and form fibrillar deposits.<sup>9</sup> These markers of A $\beta$  accumulation might not be sensitive indicators of the soluble A $\beta$  species that are thought to be particularly toxic to synaptic function. Indeed, areas of high A $\beta$  fibrillization could, in theory, reflect more-complete sequestration and neutralization of toxic A $\beta$  species.<sup>10</sup> Functional imaging studies have reported both increases and decreases in markers of functional activity, functional connectivity and glucose metabolism that are associated with genetic markers and/or increased risk of cognitive decline.<sup>11-14</sup> Volumetric MRI studies have produced paradoxical results wherein increased rates of atrophy are associated with potentially beneficial therapeutic effects.<sup>15</sup> Currently available biomarkers, therefore, are probably tracking disease progression at some level, but clearly much remains to be discovered in this realm.

Studies continue to validate the hypothesis that the presence of AD biomarkers in clinically normal older individuals—in particular, the combination of markers of amyloid and neurodegeneration—is associated with increased risk of cognitive decline. We lack the ability, however, to use these data to provide patients with an accurate prediction of the likelihood of progression to dementia. Such limitations reflect, in part, the need to better define the factors that could increase the risk of rapid decline among clinically normal A $\beta$ -positive individuals, including *APOE*  $\epsilon$ 4 genotype,<sup>16</sup> and factors that might confer some resilience to the effects of A $\beta$  pathology, such as cognitive reserve.<sup>17,18</sup> Whereas accumulating data suggest that amyloid positivity, as measured on PET, at the MCI stage is associated with a fourfold to fivefold increase in relative risk of progression to AD dementia,<sup>19</sup> very limited data in clinically normal older individuals are available to predict the likelihood of developing AD dementia in this group.<sup>4,20</sup>

Some amyloid-positive individuals may not progress to a symptomatic stage of AD within their lifetime, and quantification of the predictive value of amyloid biomarkers in the context of other demographic information will be important. An open question in the field that relates to the development of accurate prognostic measures is whether age should be taken into account in determining the threshold for biomarker positivity and the potential clinical utility of these markers. Adjustment for age is common practice when considering hippocampal volumes, but is applied variably to PET amyloid positivity, <sup>18</sup>F-fluorodeoxyglucose PET abnormalities, and CSF levels of A $\beta$ , depending on the sample and the goals of the analyses. Current estimates suggest that amyloid accumulation could predate the diagnosis of AD dementia by more than 15 years.<sup>21</sup> Consequently, individuals who become amyloid-positive in their ninth or 10<sup>th</sup> decade of life may not live long enough to develop dementia.

A related point is that age might influence the relative contribution of amyloid pathology to the rate of cognitive decline. Specifically, greater A $\beta$  accumulation might be required in younger individuals, who have relatively less age-related accumulation of neuronal injury than do older individuals, whereas even a small increase in A $\beta$  pathology could hasten

cognitive decline in very old individuals who often already have substantial neurodegeneration owing to tau or  $\alpha$ -synuclein accumulation, cerebrovascular disease, or other age-related processes. Finally, the prior probability of being amyloid-positive on the basis of age will probably influence the positive predictive value of amyloid-biomarker testing, at least in the setting of very early clinical symptoms. Less than 5% of 60-year-olds are amyloid-positive, whereas close to 50% of individuals over the age of 90 years show evidence of amyloid accumulation.<sup>21</sup>

In the context of risk prediction, the distinction between genetic risk factors for AD versus biomarkers of AD should be recognized. The rare autosomal dominant AD mutations (in the *PSEN1*, *PSEN2* and amyloid precursor protein [*APP*] genes) are thought to be essentially 100% penetrant, and relatively little uncertainty exists about whether—or even when—an individual who carries one of these mutations will develop AD dementia. By contrast, prediction of AD risk on the basis of *APOE* genotype is much more complex, as *APOE* status interacts with sex-related factors, and a small number of *APOE*  $\epsilon 4$  homozygotes do not develop dementia even very late in life.

The greatest difference between genetic risk factors and biomarker positivity is that genetic status remains constant throughout life—although the increased risk of developing dementia conferred by *APOE*  $\epsilon 4$  may be age-dependent—whereas biomarkers are dynamic as they reflect the current state of pathophysiology. Consequently, being amyloid-negative at a given time does not guarantee that an individual will not become amyloid-positive in the future. Moreover, although both genetic and  $A\beta$  markers convey information about the likelihood that an individual will enter the AD clinical trajectory at some point, markers of neurodegeneration, such as CSF phosphophorylated tau or hippocampal atrophy, are probably more useful in determining where an individual currently lies on this trajectory and when they are likely to manifest clinical symptoms of AD.

## Secondary prevention trials

A number of trials in both genetic at-risk and biomarker-positive older individuals are already being planned, including the Alzheimer's Prevention Initiative in the Colombian *PSEN1* kindred; the DIAN study in families carrying *PSEN1*, *PSEN2*, or *APP* mutations; and the Anti-Amyloid Treatment in Asymptomatic AD 'A4' trial in amyloid-positive older individuals. These trials can be considered 'secondary prevention' initiatives that aim to prevent cognitive decline in individuals showing signs that the disease process has begun in the brain.<sup>22</sup>

One of the most difficult challenges in the design of AD treatments lies in determining whether a critical window exists for therapeutic intervention with drugs that target specific disease mechanisms.<sup>23</sup> Researchers have postulated that  $A\beta$ -targeted monotherapy might be most efficacious prior to substantial neurodegeneration.<sup>24,25</sup> Whether interventions to decrease  $A\beta$  production will be adequate in the presence of substantial amyloid accumulation, together with abundant supplies of soluble  $A\beta$ , remains unknown. Ideally, primary prevention studies would be conducted in individuals at risk for AD prior to the presence of any biomarkers suggestive of pathology, but these trials would probably be more than a decade in length, and would have to enrol thousands of participants to account for variability in the rate of pathology accumulation. Given the current availability of biologically active potentially disease-modifying agents, primary prevention trials may not be practical, but we are well-positioned to begin secondary prevention trials in asymptomatic populations that are biomarker-positive and are likely to demonstrate some evidence of cognitive decline over a 3–5-year period.

Another challenge for these trials is development and validation of clinically relevant outcome measures that can be used to detect decline from ‘normal’ to subtly abnormal. Demonstration of functional decline in individuals who start clinical trials in a completely asymptomatic stage will be extremely difficult. On the basis of accumulating data from natural history biomarker studies, detection of subtle cognitive decline using sensitive composite measures of cognition seems to be feasible. In these early stages of preclinical AD, modelling of decline as a continuous process will be more powerful than time-to-event analyses involving a somewhat artificial end point, such as diagnosis of MCI. Supporting evidence from other biomarkers, including CSF levels of phosphorylated tau, and functional and structural imaging, could also be useful in demonstrating disease modification in these secondary prevention trials.

## Ethical challenges

Secondary prevention trials are among the most important studies to validate the theory that change over time in a biomarker—as opposed to change in a clinical measure, such as cognition—reflects pathology that leads to functional impairment. As valuable as these trials are, they present several important research risks that need to be addressed.<sup>26</sup> In some trials, individuals who meet research criteria for preclinical AD will be told about their biomarker results so that they can make an informed decision about participation in the trial. Disclosure of biomarker positivity raises the potential for certain risks, such as increasing anxiety or creating fear about the future. Currently, this biomarker information itself presents a challenge because its prognostic value is uncertain, given the limited longitudinal data available to date, in contrast to the decades of research findings that are available on other risk factors, such as *APOE* genotype. Such uncertainty can engender misunderstandings on the part of the participants about the implications of being biomarker-positive. Knowledge of biomarker positivity could influence subsequent neuropsychological testing or perception of clinical decline. Indeed, part of the goal of these trials is to establish the relationship between biomarker positivity and clinical outcomes.

To achieve this goal, trial protocols will need to include methods adapted from the experience of genetic testing that are designed to minimize the likelihood that a person receives information they were not ready to receive or that might be harmful to them.<sup>27</sup> Secondary prevention trials in older individuals should include eligibility criteria that reduce the likelihood of a catastrophic reaction from individuals who learn that they are biomarker-positive. These trials will need to implement an informed consent process that addresses procedures both before and after disclosure of biomarker status, including established measures to assess participant understanding.<sup>28</sup> Screening visits should include measures of anxiety and depression to identify such vulnerable participants, and the study staff who perform safety visits should assess the participants’ mood and well-being throughout the study. The current uncertainty regarding the clinical implications of the biomarker results must be carefully explained to participants.

Secondary prevention trials are likely to involve biologically active agents that entail some treatment-associated risks. Although such trials are predicated on the belief that biomarker positivity confers an increased risk of developing symptomatic AD, some participants may never progress to AD dementia but will nevertheless be exposed to potential adverse effects of preventive treatment. Judgement as to whether such therapeutic risk is acceptable should rest with each participant, because they ought to be cognitively normal with an intact capacity to assess the risk–benefit ratio and to make an informed decision about participation.



If successful, AD secondary prevention trials will identify treatments that can delay or prevent the onset of cognitive decline, but disseminating this success into clinical practice will also bring ethical and policy challenges. Individuals treated for preclinical AD will have a diagnosis and prescription on their medical record that can lead to stigma and even discrimination in the workplace, and difficulty in obtaining insurance. Indeed, this factor is a concern for individuals who participate in secondary prevention trials that require biomarker positivity for entry into the study. For example, if a medical issue related to the trial, such as amyloid-related imaging abnormalities,<sup>29</sup> occurs in the setting of anti-amyloid immunotherapy, and this result enters an individual's medical record, they may have effectively disclosed their genetic or biomarker-positive status. Existing anti-discrimination laws for genetic status may not apply to biomarker-positive older individuals, and development of public policy to protect their rights will be crucial.

## Translational challenges

Preclinical AD, like other diseases of ageing such as cardiovascular disease and osteoporosis, is likely to require long-term therapy. In addition to the expense of extended treatment, adherence to treatment presents a challenge. 6 months after hospitalization for a heart attack, as many as half of patients prescribed a statin are no longer taking the drug.<sup>30</sup> If a therapeutic trial in AD is successful, systematic monitoring of adherence and methods to maintain adherence will be a vital part of successful secondary prevention. One potential solution to several of these issues would be the development of an active immunization (a 'vaccine') for AD, perhaps targeted against multiple misfolded proteins including A $\beta$  and tau. If such a vaccine were available and could be safely administered in late middle age with 'booster' immunizations in late life, it would probably be a financially viable therapeutic avenue, and might ultimately obviate the need for biomarker screening.

Diseases of ageing share a common feature of 'dimensionality', in that the disease state is a continuum described by the risk of developing a clinical outcome such as a fracture, stroke or—in the case of AD—dementia. The features that comprise this continuum include biomarkers and other characteristics, such as age, genetics, education and other demographics, as well as health habits and comorbidities. The Framingham Risk Score for 10-year mortality after a cardiovascular event and the FRAX<sup>®</sup> score for 10-year risk of major osteoporotic fracture are examples of this dimensionality described by multi-factorial equations. This dimensionality creates the challenge, for both policymakers and practicing clinicians, of where to draw the line between those who should and those who should not receive treatment. Such a decision is guided by evidence, but clinical trials cannot cover all possible subgroups, as their entry criteria and sample sizes limit the extent to which results can be generalized to other patients. Researchers and policymakers should, therefore, develop accurate prediction models that can be updated as additional longitudinal evidence becomes available, and these models should be accessible to clinicians.<sup>31</sup>

Advancing our understanding of preclinical AD presents many distinct challenges, but they all share a common current need: resources. Large natural history studies to better define multidimensional risk, and secondary prevention trials to delay the onset of clinical symptoms will require significant financial investments. However, the cost of these studies represents a tiny fraction of the ever-increasing annual expenditure of caring for patients at the dementia stage of AD. Estimates suggest that delaying the onset of dementia by as little as 5 years would decrease US federal care costs related to AD by over 50%.<sup>32</sup> Delaying dementia onset would also decrease the innumerable personal, financial and emotional expense of AD dementia to patients and their families. Sharing of resources, both financial and intellectual, through partnerships among academia, industry, philanthropic organizations and government entities will reduce the risks of failure, but will also require sharing of the

benefits of success. Establishment of these partnerships, support of the necessary research infrastructure, and changes to public policy will require detailed national plans and international collaboration.<sup>33</sup>

## Conclusions

Numerous challenges face translation of the concept of preclinical AD into successful treatments to ultimately prevent dementia. However, given the looming epidemic of AD facing all parts of the world, we must continue to move forward with studies that resolve uncertainties regarding the validity and value of biomarker-defined preclinical stages of AD. Researchers who conduct studies that require biomarker disclosure to cognitively normal adults will need to take steps to minimize the risks of this information to the study participants. If secondary prevention trials in asymptomatic biomarker-positive populations are successful in delaying progression towards the clinical syndrome of AD, the field will need to move swiftly to ensure that biomarker testing is translated efficiently and effectively into clinical practice.

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