The pathway to secondary prevention of Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a continuum consisting of a preclinical stage that occurs decades before symptoms appear. As researchers make advances in investigating the continuum, the importance of developing drugs for secondary prevention is garnering increased discussion. For efficacious drug development for secondary prevention it is important to define what are the earliest biological stages of AD. The Alzheimer's Association Research Roundtable convened November 27 to 28, 2018 to focus on pre-clinical AD. This review will address the biological approach to defining pre-clinical AD, detection, identification of at-risk individuals, and lessons learned from trials such as A4 and TOMMORROW.

KEYWORDS
clinical trials, Alzheimer's disease, biomarkers, research roundtable

1 | INTRODUCTION

More than 50 million people worldwide are living with dementia, with Alzheimer's disease (AD) being the most frequent etiology. This number is expected to exceed 130 million by 2050 if nothing is done to slow or prevent the spectrum of dementia from developing.[1] This article focuses on strategies to address AD, acknowledging that "pure" AD (amyloid and tau pathology in isolation) is uncommon and that AD more routinely exists in the presence of other misfolded proteins (eg, alpha synuclein, TAR DNA-binding protein 43 or TDP-43) and/or vascular disease.[2] Despite tens of billions of dollars invested by various organizations over the past 20 plus years, no therapies have yet

emerged that have slowed the clinical course of AD. At the same time, significant progress has been achieved in our understanding of AD pathophysiology and on the development of soluble and imaging (and, more recently, digital) biomarkers that enable diagnosis even before there is any clinical symptomatology. The implications for the field are enormous. Most important is that an understanding of the course of the disease at such an early time point will allow for the testing of potential therapeutic modalities before there is significant pathology and at a time when therapeutic intervention may have its greatest impact.

Delaying the onset of AD has the potential not only to improve the quality of life, lessen disability, and support independent living for millions of people worldwide, but also to reduce the tremendous global economic impact of the disease. Preventing AD, however, can be accomplished only if the disease can be identified and treated before neurodegeneration has resulted in pathologies sufficient for the appearance of clinical symptomatology. Preclinical AD is the term used to describe the disease state in people who have pathological evidence of the AD process but no clinical signs and symptoms. A recent multi-state model used to forecast the prevalence of preclinical and clinical AD estimated that in 2017, a total of 46.7 million Americans had preclinical AD compared with ≈3.65 million with clinical (mild-severe AD spectrum) AD and 2.43 million with mild cognitive impairment (MCI).[3] By 2060, the number of people with preclinical AD is expected to rise to about 75 million in the United States. According to this model, preclinical AD affects 38% of the U.S. population over the age of 50. Globally, these numbers are much higher. Many people with preclinical AD, however, may not go on to develop AD dementia because of competing morbidities and other factors that are not well understood.[4] However, with improving strategies for detection and greater longevity, the number of people who progress may actually increase.

Accurate identification of preclinical AD may allow successful therapies to delay or prevent the onset of clinical and functional symptomatology that results in a diagnosis of dementia. Yet given the potential high cost of AD drugs in development, the cost of providing those drugs to all patients with preclinical AD would likely lead to a massive increase in total prescription costs, as well as for costs for detection and infusion therapy. These costs theoretically would be offset over time by a reduction in the amount spent caring for people with AD dementia, which in 2010 was estimated to total about $200 billion in the United States alone.[5]

Moreover, the shift in paradigm from treating people with clinical disease to those with preclinical disease presents challenges for drug developers, regulators, clinicians, and health systems, as well as ethical challenges and concerns about the potential for overdiagnosis and obligatory treatment that may extend out for decades, resulting in explosive prescription costs. Because only some proportion of individuals who have the pathologic (biomarker) signature of AD will progress to demonstrate memory impairment, and only a subset of those will continue to progress to the point where the memory/cognitive impairments progress to the point of impairing function ("dementia" diagnosis), there must be a clear benefit-risk profile for the treatment of biomarker-positive, clinically asymptomatic individuals at the greatest risk for developing dementia over very extended periods. For all these

reasons, the Alzheimer's Association Research Roundtable focused its Fall 2018 meeting on preclinical AD, providing a forum for experts from academia, industry, and regulatory agencies to discuss the current understanding of preclinical AD and the opportunities and challenges that must be overcome to translate that understanding into effective strategies for preventing dementia.

2 | DEFINING PRECLINICAL AD

According to the National Institute on Aging/Alzheimer's Association Research Framework, which defines AD biologically rather than clinically, preclinical AD may be defined through the use of biomarkers. In this conceptualization, biomarkers are grouped according to the neuropathologic process measured: A for amyloid, T for tau, and (N) for neurodegeneration/neuronal injury. The (N) biomarker group is placed in parentheses to indicate that although useful for staging, these measures are not specific for AD and thus are not diagnostic biomarkers. The AT(N) classification system is rooted in the hypothetical biomarker curves proposed by Jack et al. in 2010[6] and updated in 2013[7] (Figure 1), which have been generally supported by additional clinical pathological data from prospective studies in autosomal dominant autosomal dominant AD (ADAD),[8] sporadic AD, and aging cohorts.[7] These data support the hypothesis that cerebral amyloid beta (Aβ) pathology can be detected in the cerebrospinal fluid (CSF) as reduced concentration of aggregation-prone Aβ42 protein, and as aggregates in the brain by positron emission tomography (PET), 15 to 25 years before clinical symptoms appear.[9,10] Furthermore, these data indicate that tau is detectable in the CSF about 10 to 15 years before the onset of symptoms,[9,11] and closer to symptom onset by tau PET.[12] It is this period in the disease continuum that is considered preclinical, when there is only biomarker-based evidence of pathology with no obvious cognitive clinical symptoms.[13,14]

The Research Framework is flexible with regard to the addition of other putative and validated disease biomarkers, as they become available; for example, markers of decline in glucose metabolism measured with fluorodeoxyglucose PET (FDG-PET),[8-10] hippocampal atrophy or cortical thinning assessed with magnetic resonance imaging (MRI),[15] microglial activation assessed by CSF-soluble triggering receptor expressed on myeloid cells-2 (TREM2) level,[16] or neuronal injury markers such as neurofilament light.[17-19] These biomarkers may, with further validation, also be used to identify preclinical populations for secondary prevention studies.

The operationalization of the National Institute on Aging and Alzheimer's Association (NIA-AA) staging scheme was also evaluated from a clinical perspective. This led the committee to create a numerical staging scheme for individuals in the AD continuum. According to this staging system, Stages 1 and 2 represent preclinical AD. In a 2018 guidance on early AD, the U.S. Food and Drug Administration (FDA) also recognized six stages, with Stage 2 akin to early MCI, thus providing a regulatory pathway to drug approval using this staging scheme.[20]

The Mayo Clinic Study of Aging was used as a platform to discuss the implementation of a variety of clinical measures to characterize
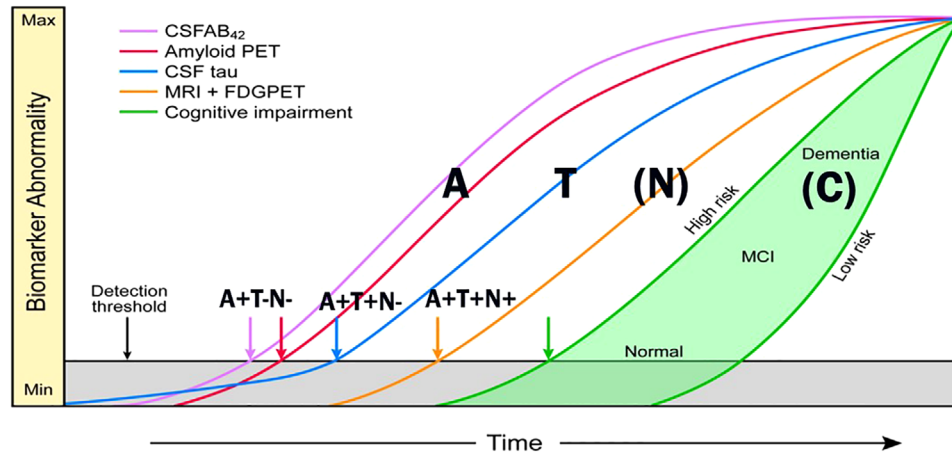
FIGURE 1 Dynamic biomarker model: modified amyloid cascade. Time-shifted curves representing the biomarkers temporal manner of pathophysiologic processes incorporating the ATN classification framework with (A) for amyloid, T for tau, (N) for neurodegeneration or neuronal injury, and additional (C) for cognitive clinical symptoms. The horizontal axis represents time and the vertical axis represents biomarker severity (abnormality) from normal (min) to abnormal (max) with the black horizontal line denoting the detection threshold.

the stages. Operationalizing Stage 2 was particularly challenging, with measures proposed to characterize the objective and subjective cognitive dimensions as well as neurobehavioral symptoms. Among these three defining characteristics, a change in cognition was the most frequently used measure to characterize people in Stage 2. When the stages were assessed for stability longitudinally, Stage 2 appeared to be the most labile. That is, over 40 percent of the persons originally classified as Stage 2 reverted to Stage 1 when re-evaluated 15 months after the initial assessment. However, in the presence of greater amyloid levels, fewer individuals reverted to Stage 1. Caution is needed to interpret these results, however, due to the many variables that come into play with regard to operationalizing the various stages. Additional research on longitudinal clinical progression is needed. Nevertheless, the staging scheme appears to be useful for delineating individuals along the cognitive continuum of persons who were amyloid positive, and this proposed scheme may be useful to further define individuals who would be eligible for randomized controlled trials in preclinical AD.

3 | GATHERING EVIDENCE TO SUPPORT TREATING AD AT THE PRECLINICAL STAGE

Secondary prevention trials for AD are those that target individuals who are clinically normal but have pathological signs indicating that the disease process is underway; that is, those with preclinical AD.[21] The Anti-Amyloid Treatment in Asymptomatic AD (A4) Trial is an example of a secondary prevention trial because it is enrolling people with evidence of elevated brain amyloid.[22] Other relevant trials currently underway include primary prevention studies in high-risk participants who have not yet manifested pathological signs of AD; The Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU) is enrolling young, cognitively healthy individuals with autosomal dominant highly penetrant mutations that cause autosomal dominant AD (ADAD) with almost 100% certainty and who are up to 15 years before

their estimated age at disease onset. The Alzheimer's Prevention Initiative (API) is also conducting a study in individuals with ADAD. The API-ADAD trial will enroll asymptomatic *PSEN1* E280A mutation carriers from family kindred with ADAD in Colombia.[23] DIAN-TU is also planning a Primary Prevention study that will enroll participants 18 years and older who are without evidence of Aβ-PET pathology. The development of the DIAN-TU platform trial will allow for enrollment of multiple intervention arms simultaneously and consecutively and the sharing of placebo data between different interventions in order to maximize trial efficiency and power.[24]

3.1 | The challenge of detecting preclinical AD

Imaging and fluid biomarkers may be useful in detecting preclinical AD. Blood-based biomarkers offer substantial advantages for screening large populations due to their reduced invasiveness, lower costs, and increased acceptance by patients, but improving sensitivity and reliability is key to recognizing these advantages.[25] Several large international consortia have been established to advance the development of blood-based biomarkers.[26-29] Cognitive changes, sleep quality, and behavior may also offer opportunities to detect preclinical AD, as discussed below.

3.1.1 | Biomarkers of preclinical AD

Imaging biomarkers that may be helpful in identifying preclinical AD in individuals who are cognitively unimpaired include amyloid and tau aggregation load as determined using PET, and neurodegeneration and neuronal injury as measured by structural magnetic resonance imaging (MRI) and glucose hypometabolism as measured by FDG-PET. Three amyloid PET ligands—florbetapir, florbetaben, and flutemetamol—are currently approved, and a new ligand, fluselenamyl,

is in development.[30-33] The three approved agents are specific for $A\beta$ plaques or $A\beta$ in the vessel walls, and images produced from PET scans with all three ligands correlate with autopsy findings. However, known limits to the sensitivity of each agent mean that a negative scan does not prove the absence of $A\beta$ deposits in all cases.

Several tau radioligands are currently being evaluated in clinical research studies. The most well studied at this point is flortaucipir (18F-AV-1451), which binds specifically to 3R and 4R tau (the isoforms that make up the paired helical filaments in the AD brain), generally follows the topographic distribution of neurofibrillary tangles described in typical AD by Braak et al., and produces images that show binding in areas of the brain where neurodegeneration is associated with cognitive impairment.[34] It is currently under review by the FDA. As is the case with amyloid PET, tau PET has sensitivity limitations as well as off-target binding, which may compromise diagnostic accuracy.[35] Measures of neurodegeneration, atrophy, and hypometabolism reflect loss (MRI) or dysfunction (FDG-PET) of dendritic spines, synapses, and neurons, but neither measure is specific for AD; however, their prognostic value increases when combined with biomarkers of amyloid and tau.

CSF biomarkers may also be used as markers of A, T, and (N). CSF $A\beta42$ is well accepted as a marker of the pathophysiologic state associated with development of senile plaque pathology.[36] Low levels correlate well with amyloid PET[37-38] with a concordance of ≈90%, which increases as the disease progresses.[39] CSF $A\beta42$ declines to its minimum level at least 5 to 10 years before dementia develops, indicating its usefulness as a preclinical marker[40-41]; however, it is less useful at the symptomatic stage and may have greater limits as an outcome measure in preclinical AD trials. CSF $A\beta42$ may also be reduced in the presence of neuroinflammation, normal pressure hydrocephalus, and other disease states; and there may also be constitutively low $A\beta$ producers who are close to the $A\beta42$ cut point for positivity. Fortunately, using the ratio of CSF $A\beta42/A\beta40$ corrects for this problem and provides an accurate biomarker for early AD,[42] which is easy to interpret, has a robust correlation to pathology, becomes clearly abnormal, and does not change over time in symptomatic disease. Moreover, in recent years, fully automated assays with low variation have become available, along with standardized reference methods and materials.

CSF tau is more complicated. CSF total tau (T-tau) and phosphorylated tau (P-tau) are strongly associated with AD.[43] A recent study of the relationship between CSF T-tau and P-tau and tau PET using the ligand flortaucipir (18F-AV-1451) showed that CSF P-tau and T-tau are elevated in preclinical AD and may appear even before the deposition of tau.[44] The lack of correlation with tau-PET and post-mortem pathology suggests that CSF tau may reflect a disturbance in disease homeostasis rather than the pathologic burden of tau deposits.

Neurofilament light (NFL) protein is a component of the neural cytoskeleton. Its presence in the CSF reflects damage or degeneration of neurons.[45] Elevated levels of CSF NFL are seen in many neurodegenerative diseases including AD,[46] where CSF NFL concentrations begin to increase in the early stages of disease and continue to increase over time.[47] High levels are associated with disease progression, more pronounced cognitive decline, and faster brain atrophy.

NFL has also shown promise as a plasma biomarker of neurodegeneration for AD. Several studies have shown that plasma NFL correlates with CSF NFL and neuroimaging markers as an indicator of neurodegeneration across the AD continuum, is higher in people with both MCI and AD, even after correcting for age,[48] and is associated with cognitive decline and neuroimaging biomarkers of AD.[18,19,49] Serum NFL concentration increases 5 to 15 years prior to clinical disease onset in familial AD and may thus be an easily accessible biomarker for onset of neurodegeneration.[19]

Other plasma biomarkers have also shown some promise. Blood amyloid biomarkers results have been somewhat inconsistent in the literature[50,51]; however, plasma $A\beta42/40$ ratio measured by mass spectrometry has been shown to provide a sensitive and reliable measure of amyloid status that predicts future progression to positive amyloid PET and correlates with CSF $A\beta42/40$.[51-52] Plasma T-tau is elevated in persons with AD as well as other brain disorders,[53-55] and plasma P-tau has been shown to be a sensitive and specific predictor of elevated brain $A\beta$, which suggests it may be useful for screening,[56] although more research is needed on the topic.

Plasma is also being tested with explorative mass spectrometry approaches to identify changes in the proteome that reflect different disease states.[57] The Accelerating Medicines Partnership for AD (AMP-AD) has undertaken a multi-institute, large-scale proteomics approach to profile proteomic changes across the AD continuum. Designed to provide a deeper understanding of the molecular mechanisms underlying disease progression, these studies may also identify biomarkers that can be used in clinical trials and clinically.

Roundtable participants stressed the need to be realistic about the utility of blood biomarkers. They may be ideal for large-scale screening in primary care clinics where they can reach broad populations to rule out $A\beta$ positivity. However, for other contexts of use, such as a biomarker of progression, more research is needed. The infrastructure is in place to validate several screening markers; however, it will be necessary to identify and quantify sources of variability.

3.1.2 | Psychometric approaches to detecting preclinical AD

By definition, cognition remains in norm.al limits in older adults classified with preclinical AD. Despite the absence of abnormality, multiple longitudinal studies have shown that in cognitively normal individuals, positive $A\beta$ biomarkers are associated with increased risk of progression to MCI and dementia.[58-61] Furthermore, even before clinical disease progression, serial neuropsychological assessments show positive $A\beta$ biomarkers to be associated with subtle (i.e., Cohen's d = ~0.5) but relentless decline in cognition when compared to change in matched $A\beta$-negative controls.

In preclinical AD, amyloid-related cognitive decline is most evident in episodic memory, although there is also evidence for decline in other domains, including attention, language, and visuospatial function and when such measures of cognition are combined into constructs such as global cognitive function.[62] Strong associations between cognitive

decline and the presence of abnormal biomarkers makes cognitive outcome measures optimal end points for clinical trials of drugs designed to forestall the development of AD. The Preclinical Alzheimer's Cognitive Composite (PACC) is a global outcome measure developed in accordance with recommendations from the FDA that cognitive changes used to assess drug effects in preclinical AD reflect performance across multiple aspects of cognition as well as considering the importance of memory decline in the disease. PACC scores and similar cognitive composites are being used currently as cognitive end points in the A4 and Generation studies. PACC scores can be derived from the neuropsychological batteries used in many of the large natural history studies, and in each case such scores have been shown to adequately capture progression of disease throughout the preclinical stages.[63]

3.1.3 | Subjective cognitive decline and mild behavioral impairment in preclinical AD

Subjective cognitive decline (SCD) is associated with an increased risk of progression to MCI and dementia and may be one of the first cognitive symptoms of AD, associated with biomarker positivity.[64] SCD is detectable in preclinical AD using self- and informant-reported subjective memory questionnaires and neuropsychological assessments, including tools such as the PACC, ECog, Blessed memory test, and Cognitive Change Index (CCI).[65-67] SCD-plus criteria include complaints of memory impairment over other domains, onset of cognitive complaints within the last 5 years or over the age of 60, concerns over cognitive decline worse than others of a similar age, confirmation of cognitive decline by an informant, and apolipoprotein E gene (*APOE*) ε4 carriage; and increase the likelihood that SCD reflects preclinical AD.[68] However, SCD may also be associated with psychiatric symptoms including depression and anxiety, the presence of which may confound the assessment of SCD.[66]

Changes in behavior and personality, better framed as neuropsychiatric symptoms (NPS), are included in the diagnostic criteria for dementia, including dementia of the Alzheimer's type, frontotemporal dementia (FTD), and vascular dementia.[69] Evidence suggests, however, that NPS emerge frequently in advance of cognitive impairment. A recent analysis of National Alzheimer's Coordinating Center data demonstrated that of those participants who developed AD, 30% developed NPS in advance of MCI.[70] Patients who develop dementia are often given psychiatric diagnoses for what are early manifestations of neurodegenerative disease[71-73]; thus better awareness of NPS as potential markers of incident cognitive decline and dementia is required.

Mild behavioral impairment (MBI) is a validated syndrome that characterizes these later-life acquired and sustained NPS and frames them as an at-risk state for incident cognitive decline and dementia. For some preclinical individuals, MBI is the index manifestation of neurodegeneration, observed in advance of cognitive impairment.[73-75] MBI is associated with faster cognitive decline in a large community population with normal cognition[76] and has shown to significantly increase the progression rate to dementia in those with normal cognition or MCI.[77] MBI has demonstrated a higher conversion rate to dementia

than a psychiatric comparator group consisting of late-life psychiatric disorders,[78] highlighting the distinction between MBI and psychiatric disorders.[72] Thus, detecting early the NPS that constitute MBI may aid in earlier detection of dementia at the preclinical or prodromal phase, in advance of or in addition to cognitive impairment.

Further exploration of MBI prognostication for incident cognitive decline and dementia is part of the research agenda in this field,[79] but early results suggest that MBI may be an easily implemented approach to capture an enriched biomarker-positive group of older adults with normal cognition, providing a chance for earlier intervention and enrollment in prevention trials.[79] Thus, screening for emergent neuropsychiatric symptoms may provide a simple and efficient method to identify a high-risk population for dementia.

3.1.4 | Sleep quality and preclinical AD

Poor sleep is associated with decreased cognitive performance in older adults,[80,81] and excessive daytime sleepiness (EDS) was shown to be predictive of cognitive decline in the French Three City Study.[82] Moreover, in the Baltimore Longitudinal Study of Aging, EDS was associated with amyloid positivity.[83] Short sleep duration (<6 hours per night) is associated with greater amyloid burden[84]; and prolonged sleep duration (>9 hours per night) has been shown to be associated with an increased risk of dementia,[85] further indicating that disrupted sleep may be an early marker of neurodegeneration.

In preclinical AD, individuals with the lowest sleep efficiency compared to those with the best sleep efficiency were 5 times more likely to have elevated Aβ.[86] Aβ pathology has also been associated with longer sleep latency.[87] Among those at risk for AD, worse subjective sleep quality, increased sleep problems, and EDS were shown to be associated with increased Aβ and tau[86,87]; and baseline EDS was associated with increased Aβ accumulation in the nondemented elderly, suggesting that the presence of EDS indicates increased vulnerability to pathological changes associated with AD.[88] Because the association between sleep and AD appears to be bidirectional, treating late-life sleep disturbance may help prevent or slow the development of AD.

3.1.5 | Polygenic risk prediction of preclinical AD

Genetic data obtained in genome-wide association studies (GWAS) by the International Genomics of Alzheimer's Project (IGAP) has been used to calculate polygenic risk scores (PRS) that predict AD with a high degree of accuracy.[89] PRS can be used to identify candidates for trials and may, with further validation, be useful to inform treatment decisions and help patients and families plan for the future. A caveat in the use of PRS is that they are applicable only to the population from which they were derived, which currently means people of European descent. They also should be used in combination with other disease indices.

Similar to PRS, polygenic hazard scores (PHSs) predict absolute age-related risk, which may be more useful in identifying people in the preclinical stage of disease. Desikan et al. developed a PHS that

retrospectively predicted age of onset and rate of progression to AD in asymptomatic older adults and showed that it correlates with biomarker and neuropathology measures.[90] They went on to show that the PHS could be used prospectively to predict rate of progression to AD in individuals with both preclinical AD and MCI, and that the PHS was more strongly predictive compared to *APOE* status alone.[91] In addition, they showed that the combination of PHS and biomarkers status predicted accelerated clinical progression.[92] PHS may thus be useful both to enrich preclinical AD trials with biomarker-positive individuals and as a stratification marker in clinical trials.

3.1.6 | Digital biomarkers

Digital biomarkers have also attracted attention as potentially useful in the detection of subtle cognitive and functional changes in the early stages of AD and may also be useful as sensitive secondary end points in clinical trials. Wearable devices, smartphones, and infrared sensors are all capable of capturing continuous high-dimensional data that reflect health-related aspects of daily life (eg, walking, remembering to take medication, using a computer, sleeping, and social interactions), which are inherently ecologically valid and meaningful. These measures have not yet been widely deployed in clinical research, and increased efforts are needed to more fully understand how best to deploy and integrate them into trials as well as interpret and analyze data with confidence.[93-97] There is great promise that digital biomarkers could identify those at high risk of developing clinical AD for primary prevention and trial enrichment or be used for sensitive secondary end points in clinical trials. The National Institutes of Health and Veterans Administration (NIH-VA) supported CART (Collaborative Aging Research using Technology) platform is addressing this need, providing an open, technology-agnostic, end-to-end system for the research community.[98] In Europe, academic and industrial leaders in the field of AD recently announced the launch of "RADAR-AD" (Remote Assessment of Disease And Relapse—AD). The collaborative research program aims to develop technologies that remotely identify and measure "digital biomarkers" to assess the progression of early AD.

3.1.7 | Participant registries

Patient registries are critical for engaging participants in the clinical trial process and recruiting and enrolling them in trials. For preclinical prevention AD trials, large cohorts need to be recruited, assessed, and monitored longitudinally through a variety of approaches.

One such registry is the Brain Health Registry (BHR), which was established in 2014 at the University of California, San Francisco as an online project to recruit individuals interested in brain health and, potentially, in clinical studies of AD and other brain disorders. BHR has enrolled over 60,000 participants, with the majority in their 50s and 60s, with thousands over the age of 70. More than half of those enrolled have a family history of AD. Among those age 55 and older, nearly half have memory concerns. BHR uses a computerized test battery[99] val-

idated for online administration. This test used longitudinally allows BHR to identify individuals with declining cognition who may be eligible and appropriate for prevention trials, and then refer willing individuals to trial sites.

3.2 | Ethical and regulatory aspects of developing treatments for preclinical AD

Both the European Medicines Agency (EMA) and FDA have published guidelines for testing compounds in early AD,[100,101] and both of these guidelines rely heavily on biomarkers, applied in various contexts of use, which can include selecting patients, capturing disease progression, measuring drug exposure, or demonstrating drug effects.[100,101] Moreover, both agencies emphasize the need for precompetitive sharing of rigorously collected standardized data across the AD scientific community in order to understand disease progression and its relevant sources of variability. In Japan, drugs that target preclinical AD might be evaluated through their "Conditional Early Approval System" that aims to put highly useful and effective drugs into practice as quickly as possible. Early approval may rely on biomarkers as primary end points, only if a correlation has been demonstrated between the biomarker and a clinical effect.

3.2.1 | Bioethical considerations in the translation of preclinical AD from research into practice

New criteria for defining preclinical AD are introducing ethical challenges because cognitively normal people may suddenly come face-to-face with terms such as "preclinical Alzheimer's pathological change." An adjunct to the A4 Study, SOKRATES (Study of Knowledge and Reactions to Amyloid Testing) is exploring the experience of learning one's amyloid status.[102] Core aspects of this experience are concerns about how the level of amyloid corresponds to the risk of decline, how to interpret subtle cognitive changes, and how elevated amyloid might affect one's relationship with others, plans for the future, and feelings of self-control and self-determination.

3.3 | Moving forward: lessons learned from secondary prevention trials in preclinical AD

In 2011, investigators from three academic-led prevention initiatives—DIAN, A4, and API—came together to form the Collaboration for Alzheimer's Prevention (CAP). The aim of the umbrella group was to harmonize efforts, avoid duplication, share data, and jointly seek regulatory guidance. Subsequently the group was expanded to include the industry-funded TOMMORROW trial and the European Prevention of Alzheimer's Disease (EPAD). In 2016, CAP published principles to guide data and sample sharing in preclinical AD trials.[103] Sponsors and companies involved in these trials have agreed to these principles, as have many other sponsors who are conducting large clinical trials in the AD space.

Continued efforts are also needed to address constraints to data sharing, including concerns about (1) maintaining scientific integrity of trials, (2) not compromising the ability of a study to withstand independent scientific scrutiny, and (3) maintaining the confidentiality of trial participants, particularly those with autosomal dominant mutations or genetic risk factors. Functional platforms are also needed to ensure data interoperability.

The main challenge, however, is finding drugs that effectively halt or forestall the development of AD symptoms. Despite many disappointing trial results, there remains optimism that an effective treatment is within reach and that prevention trials in AD will play a critical role in identifying such effective treatments. Moreover, there is broad support for continued efforts at lifestyle factors that decrease the burden of AD in the population at large, a blood test to efficiently and inexpensively detect preclinical AD and qualify biomarkers and other end points in order to use accelerated approval mechanisms and to address other scientific, regulatory, financial, ethical, social, organizational, and logistical challenges.

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