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Alzheimer's & Dementia
Translational Research & Clinical Interventions

PERSPECTIVE

Operationalizing selection criteria for clinical trials in Alzheimer's disease: Biomarker and clinical considerations

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Abstract

Alzheimer's disease (AD) staging criteria lack standardized, empirical description. Well-defined AD staging criteria are an important consideration in protocol design, influencing a more standardized inclusion/exclusion criteria and defining what constitutes meaningful differentiation among the stages. However, many trials are being designed on the basis of biomarker features and the two need to be coordinated. The Alzheimer's Association Research Roundtable (AARR) Spring 2021 meeting discussed the implementation of preclinical AD staging criteria, and provided recommendations for how they may best be incorporated into clinical trials research. Discussion also included what currently available tools for global clinical trials may best define populations in preclinical AD trials, and if are we able to differentiate preclinical from clinical stages of the disease. Well-defined AD staging criteria are key to improving early detection, diagnostics, clinical trial enrollment, and identifying statistically significant clinical changes, and researchers discussed how emerging blood biomarkers may help with more efficient screening in preclinical stages.

KEYWORDS
Alzheimer's disease, amyloid, biomarkers, clinical trials, cognition, cognitive impairment, dementia, mild cognitive impairment, tau

1 | INTRODUCTION

During only the past few years, the definition of Alzheimer's disease (AD) has shifted from a syndromal description to a biological construct.[1] Amyloid beta (Aβ) protein deposition in senile plaques in brain parenchyma and phosphorylated tau (p-tau) deposition in neurofibrillary tangles in cerebral neurons characterize AD as a neurodegenerative disease that can result in dementia.[2–3] Impairment is considered distinct from etiology. This paradigm shift has helped researchers better understand the mechanisms of AD and its progression. Indeed, this refocus has expedited the development and evaluation of disease-modifying interventions that aim at biologically defined targets.

Given that the pathophysiological processes of AD occur well before the manifestation of clinical findings, the global AD research community has been directing efforts at early-stage, even presymptomatic, intervention.[4] Suspending, terminating, or even reversing the initial neurodegeneration that results in clinical deficits is, of course, the objective. Accordingly, clinical trialists now endeavor to diagnose AD in the preclinical stages, well before cognitive impairment or dementia

develops. Establishing criteria to select appropriate study populations for early-intervention clinical trials is at the forefront of these studies. Simultaneously, researchers are working toward standardizing existing biomarkers (e.g., neuroimaging and cerebrospinal fluid [CSF] analysis) and seeking new ones to assist in identifying these early stages in the AD continuum. Blood-based biomarkers, the newest and, arguably, most exciting tests, may soon be available to guide the diagnostic process in clinical practice. Without biomarker evidence of amyloid and tau pathology, early-stage clinical symptoms of AD cannot be attributable to the effects of AD pathology. Melding early-stage AD clinical criteria and early-stage AD biomarker characterization needs further research and understanding.

Consequently, stakeholders in these enterprises convened virtually during the Spring 2021 Alzheimer's Association Research Roundtable (AARR). Distinguished participants included leaders in the pharmaceutical industry, the global academic community, US and European regulatory agencies, clinical practice, and policy making. Presenters and panelists discussed cutting-edge efforts and unpublished research data and offered unique perspectives on the task of operationalizing (defining, so as to practically measure) selection criteria for AD clinical trials and biomarker implementation as it relates to National Institute on Aging and the Alzheimer's Association (NIA-AA) stages I and II.

RESAERCH IN CONTEXT

1. **Systematic review**: The Alzheimer's Association convened a roundtable discussion to discuss the implementation of preclinical Alzheimer's disease (AD) staging criteria, and provide recommendations for how they may best be incorporated into clinical trials research.
2. **Interpretation**: Emerging biomarkers have the potential for use in clinical trial enrollment and will improve the efficiency of early-stage AD clinical trials.
3. **Future directions**: Emerging biomarkers and clinical characteristics have demonstrated evidence of improved prediction of decline and offer the opportunity for future research.

2 | CLINICAL CHARACTERISTICS OF AD NUMERIC STAGES I AND II

Pivotal in the Roundtable discussions were the NIA-AA Research Framework workgroup. In 2018, the workgroup published a key recommendation: AD should no longer be regarded as three distinct compartments—cognitively unimpaired, mild cognitive impairment (MCI), and dementia—but, rather, a continuum. This six-stage numeric system (Figure 1) better captured the progression of AD, with stages 1 and 2 corresponding to, in general, cognitively unimpaired (preclinical) stages of AD and stage 3 corresponding to MCI.[1]

Stages 1 and 2 were the focus of the Spring 2021 AARR, given early clinical (i.e., cognitive or neurobehavioral) evidence of symptoms attributable to the AD continuum pathology that can be detected. Individuals in stage 2 may be transitioning toward cognitive impairment and may be a target population for early-intervention trials.[5] Thus, it is advantageous to well define stage 2 cognitively. Characterizing stage 2 biologically also is beneficial, because, typically, in early stages of the AD continuum, abnormal AD biomarkers appear in asymptomatic individuals. As the disease progresses, biomarker changes increase, and subtle cognitive decline appears.

Improving the clarity of stages 1 and 2 has profound implications for clinical trialists who design trials in conjunction with the Food and Drug Administration (FDA). The FDA defines stage 2 a bit differently than the NIA-AA. The latter specifies longitudinal cognitive change that is subjective or objective, but the FDA does not mandate this longitudinal change; rather, only subtle detectable abnormalities on sensitive neuropsychological measures.[6]

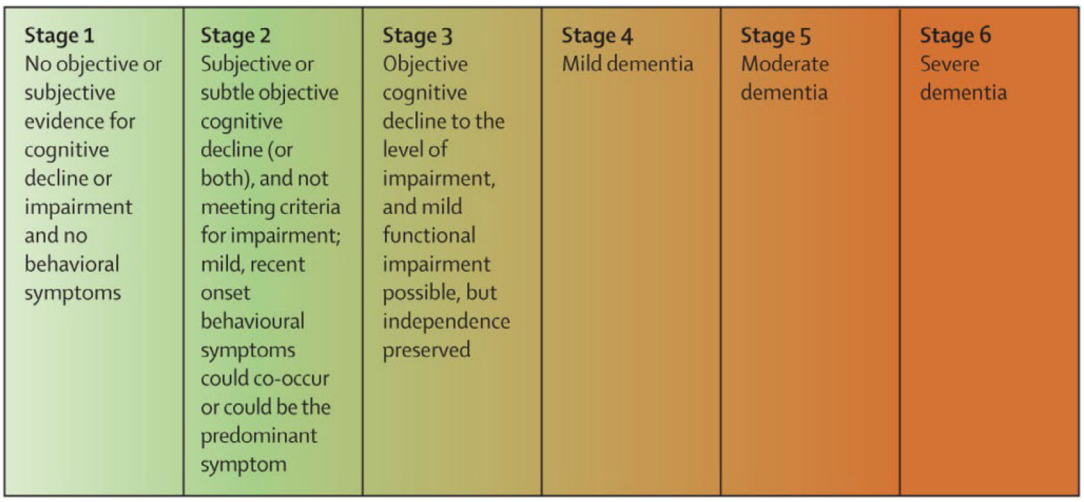

FIGURE 1 Numeric clinical staging applicable only to individuals in the Alzheimer's disease continuum (adapted from Jack et al.[1])

The Mayo Clinic Study of Aging has operationalized the NIA-AA six stages. This operationalization considers cross-sectional objective cognition (OBJ), cross-sectional function (FXN), subjective cognitive decline (SCD), objective cognitive change (ΔOBJ; a slope change of cognition, memory, and attention), and neurobehavioral symptoms (NBS) decline. In addition, the numeric system can monitor subtle changes in cognition better than the three-category system and allows for a common language among researchers. Moreover, the Roundtable discussion highlighted the numeric system, which facilitates the targeting of certain AD pathways in intervention trials. All these features nicely position the new staging system for use in outcome-measure selection in interventional trials; evaluation of novel therapies; and, optimistically, a cure for AD.[1,5]

2.1 | Objective cognitive decline

The Roundtable discussed operationalizing numeric stages 1 and 2, which represent the preclinical stages of AD.[1] A better understanding of these early stages can assist in secondary prevention of the disease. To be sure, a major focus in secondary-prevention trials has been assessing SCD, which occurs at the transitional AD stage, the stage between cognitively unimpaired and MCI (i.e., numeric stage 2).

It is imperative that an intervention be able to show or predict clinical benefit, thus the need to enroll participants who are most likely to demonstrate measurable transitional cognitive change during the course of a secondary-prevention trial. Many individuals who have a slowly progressing AD and who are in the preclinical stages may not progress over the course of a clinical trial, limiting the ability of the trial to efficiently determine clinically meaningful treatment effects. For example, the Harvard Aging Brain Study (HABS) group has shown that, when following clinically normal participants on the biomarker-defined (elevated amyloid positron emission tomography [PET]) AD trajectory, fewer than one third progress to clinical impairment during a 3-year period. More specifically, combining data from HABS, the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL), and the Alzheimer's Disease Neuroimaging Initiative (ADNI), rates of progression to MCI ranged from 20% to 32% during a 3-year period among those with preclinical AD.[7] Determining a cognitive benefit during a 3- to 4-year trial would be very challenging if there were many stage 1 participants, that is, participants not exhibiting transitional cognitive decline. Furthermore, biomarker staging (e.g., amyloid [A]+, tau [T]+ vs. A+T−) and operationalized clinical staging may improve prediction of those at highest risk for transitional cognitive decline. Future inquiries worth investigating are determining whether specific cut points for decline or diminished practice effects operationalize and harmonize well across test populations.

2.2 | Subjective cognitive decline

It is also necessary to consider SCD in operationalizing stages 1 and 2 AD.[8] The term SCD was coined in 2014 to refer to cognitively unimpaired individuals who are concerned they have reduced cognitive function. Research criteria for SCD, published in 2014, require SCD to be a personal experience, an individual feeling of persistent—not occasional—decline in cognitive capacity, compared to a previously normal status. SCD can be challenging to measure and must not be related to an acute event. The research criteria require that individuals be assessed as normal on standardized cognitive testing, adjusted for age, sex, and education.[9] Jessen et al.[10] compiled a list of features that increase the risk of cognitive decline and the likelihood of amyloid positivity in the brain (as determined by CSF Aβ42); this is called SCD plus. It is a dynamic list that may be updated as new evidence arises. Currently, it includes subjective decline in memory irrespective of function in other cognitive domains, onset of SCD within the past 5 years, onset of SCD at age $\geq$ 60, worry associated with SCD, persistence of SCD over time, medical-help seeking, and confirmation of cognitive decline by an observer.

SCD assessment is challenging, as no gold standard tool for measuring SCD exists. The Subjective Cognitive Decline Initiative (SCD-I) found that 34 different self-report measurement scales were used in 19 different SCD studies representing eight countries and five languages; little overlap existed among measures. The Initiative advocates for international collaboration in the pooling of data to promote harmonization and consistency in the measurement of SCD.[11] Some researchers have concluded that SCD is not a suitable longitudinal outcome measure in AD trials because, with dementia, SCD decreases over time due to increasing anosognosia. SCD may be better applied to case identification rather than follow-up or outcome measures. However, much enthusiasm exists in probing SCD's potential role as a harbinger of neurodegenerative disorders. Alongside biomarker detection of neurodegenerative disease, SCD could become relevant in early AD intervention.[10]

2.3 | Neuropsychiatric symptoms

Research has emerged to help our understanding of neurobehavioral and neuropsychiatric symptoms within the Research Framework. As early as 2014, the Mayo Clinic Study of Aging published their results of a prospective cohort study that revealed that, after adjusting for age, sex, education, and medical comorbidity in cognitively normal persons, baseline non-psychotic neuropsychiatric symptoms (agitation, apathy, anxiety, irritability, and depression) were significant predictors of incident MCI.[12] More recently, mining of the Amsterdam Dementia Cohort data revealed a high prevalence of neurobehavioral symptoms, particularly apathy and mood symptoms, in people with SCD and an amyloid-positive biomarker.[13]

The Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART-AA) developed the mild behavioral impairment (MBI) criteria, which are widely used in AD neuropsychiatric research. The criteria describe changes in behavior or personality with emergence at $\geq$ 50 years of age and persistence for $\geq$ 6 months. This construct has five domains: interest/motivation/drive, mood/anxiety, irritability, impulse control, and suspicious thoughts.[14]

Using these criteria, the Platform for Research Online to Investigate Genetics and Cognition in Aging (PROTECT) data revealed MBI to be prevalent in 9% of a cognitively normal population ($n = 10,000$) aged > 50.[15]

A number of studies suggest that MBI predicts either incident MCI or incident dementia. Not all these studies excluded people who had concurrent cognitive impairment; yet, the literature shows that MBI is a predictor of more significant cognitive impairment. The Brain Health Registry generated one such study: an 800-participant study that compared at several different thresholds people with and without MBI. Those with MBI had poorer memory span, poorer reverse memory span, longer Trail Making Test completion time, and more Trail Making Test errors.[16] In a larger longitudinal cohort from the PROTECT study of almost 1000 people with MBI in the absence of MCI, there was significantly greater deterioration in attention and working memory during a 12-month period in people with MBI compared to the 9000 people without MBI.[15] This highlights the important pattern of subtle but progressive neuropsychological impairments in people who met the criteria for MBI.

Evidence also is accumulating suggesting that MBI is associated with biomarker changes, such as PET amyloid burden. The Translational Biomarkers in Aging and Dementia (TRIAD) study observed such an association; however, importantly, it did *not* find an association between MBI and tau neuroimaging biomarkers.[17] Conversely, the Swedish BioFINDER2 study found an association between MBI and tau PET in the medial temporal cortex and also with CSF p-tau.[18] A Canadian study observed plasma neurofilament light changes occurring over a 2-year period were associated with MBI with researchers concluding that "MBI is a clinical proxy of early-phase neurodegeneration with putative utility in identifying those at dementia risk."[19]

Longer-duration follow-up studies should be conducted, and longitudinal measurement of biomarkers for AD and neurodegeneration is needed. People with MBI may represent an important group of individuals with a high likelihood of being biomarker positive and at increased risk of progressive cognitive decline, who may be easily identified with a brief screening tool.

3 | BIOMARKERS FOR AD

Alzheimer's disease (AD) imaging and biofluid (CSF and blood) biomarkers represent a continuous measurement but, using a variety of approaches, each can be dichotomized based on the association with AD pathology into normal (+) or abnormal (–) via application of cut points. Regarding amyloid accumulation, "all or nothing" does not reflect the pathology of the disease. The Mayo Clinic (Florida and Minnesota) demonstrated this by comparing Pittsburgh compound B (PiB) PET with Thal pathology (the pattern of progressive amyloid plaque deposition in AD) in different stages of amyloid pathology at autopsy. The study showed that cortical PiB PET can detect the progressive accumulation witnessed in the Thal amyloid phases. That correlation has favorable implications for PiB PET use in screening participants for enrollment in clinical trials.[20]

Highly correlated are PET amyloid and CSF amyloid measurements, as shown in several studies assessing the agreement between cerebral amyloidosis (determined via amyloid PET) and CSF Aβ42/40.[21–23] "Amyloid positivity" is challenging to define; thus, how it is defined will determine a study cohort. If performed thoughtfully, however, very good correlations between PET amyloid and CSF amyloid measures can emerge and cut points can be used to establish the presence of amyloid pathology in the earlier stages of the disease. Interlaboratory standardization is well conducted for CSF AD biomarkers, due to the availability of certified reference materials and methods and automated platforms calibrated against those.[24] Amyloid PET could inform on early development of AD pathology.[25–26] But, as AD research increasingly focuses on earlier stages of the disease in which lower levels of amyloid are being measured, caution must be taken, because within a single biomarker, platforms and measurements are not immediately interchangeable.

3.1 | PET tau and CSF tau

A number of radiotracers are available for research purposes for imaging tau protein, but flortaucipir is the only tau tracer FDA approved for clinical use in the United States. However, it should be noted that tau PET tracers have low uptake in most non-AD tauopathies during the dementia phase of the disease.[27,26] Recently published studies suggested that PET imaging with flortaucipir could be used to identify the density and distribution of AD-type tau pathology and the presence of high levels of AD neuropathological change, supporting a neuropathological diagnosis of AD.[28–29] Using a weighted target volume of interest derived by multi-block barycentric discriminate analysis (MUBADA) on an independent set of AD and clinically normal subjects, [30] virtually all participants in the study who were staged at neuropathology Braak stage V or VI had increased levels of flortaucipir uptake in the brain.[31] Though these are the later Braak stages, rather than the earlier ones, it is important to remember that in the earlier Braak stages of AD, the actual density of tau tangles sometimes can be quite minor, even in the medial temporal lobe. When detecting tau aggregates in AD, researchers must consider where they measure the tau PET signal. Accordingly, a Lund University group performed event-based modeling to investigate where tau deposition in the brain first occurs. *Post mortem* studies have shown that, in most cases, the transentorhinal region (area 35) of the medial temporal lobe was the first cortical site where neurofibrillary tangles appeared. The group's tau PET imaging results corroborated this. Entorhinal cortex and area 35 showed the earliest signs of tau accumulation followed by the anterior and posterior hippocampus, amygdala, area 36, and the parahippocampal cortex.[32]

3.2 | Plasma amyloid and plasma tau

In the last several years, plasma biomarkers have made advances in demonstrating consistent performance and applicability across the stages of AD. Despite the advances in analytical performance, the

Syndromal Cognitive Stage				
Biomarker Profile		Cognitively unimpaired	MCI	dementia
	$A^-T^-(N)^-$	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
	$A^+T^-(N)^-$	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
	$A^+T^-(N)^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
	$A^+T^+(N)^-$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI (Prodromal AD)	Alzheimer's disease with dementia
	$A^+T^+(N)^+$			

FIGURE 2 Syndromal staging combined with biomarker staging.[1] A, amyloid; AD, Alzheimer's disease; MCI, mild cognitive impairment; N, neurodegeneration; T, tau

plasma Aβ42/40 ratio changes only about 10% to 20% between amyloid-negative and amyloid-positive subjects.[33–34] If plasma Aβ assays with mass spectrometry or enzyme-linked immunosorbent assay can achieve the analytical performance to detect such a small change, they may have utility to enrich for the earliest pathology-staged subjects A+T– but will require amyloid PET to confirm pathology in the early stages of AD.[35] This likely will be the case for plasma p-tau assays, as well.

Plasma total p-tau is more encouraging than plasma amyloid when differentiating preclinical AD (defined as A+T+ by CSF biomarkers) from amyloid-negative cognitively unimpaired, plasma isoform p-tau increases 50% to 300% in the earliest stages of AD. Depending on the assay, p-tau 217 had an area under the curve of 0.90 and was significantly better than competing imaging and fluid biomarkers.[36] Multiple independent neuropathology cohort studies independently demonstrate an association of plasma p-tau with Braak stage, as well as good diagnostic accuracy for phosphorylated isoforms of tau for the identification of AD pathology.[37–39] A recent analysis of BioFINDER data and data from the University of California, San Francisco revealed that abnormal or higher levels of plasma p-tau were associated with increased rates of cognitive decline and that lower levels of plasma p-tau were associated with reduced progression to AD or to non-AD conditions.[39,40] Together, these data demonstrate that plasma p-tau assays can achieve suitable performance in early stages of AD to identify subjects with the likelihood of being A+T+ and with an increased risk of cognitive decline over 2 years without the need for PET confirmation. The use of p-tau in screening will be valuable for clinical trial screening efficiency and study power.

Combining multiple biomarkers may complement each other, reduce the percentage of false positives, and increase patient enrichment for clinical trial enrollment. Sharing data so that researchers can analyze larger data sets with more variability in patient populations can help detect relationships. Standardization will be important and helpful to perform analyses of those larger data sets. Integrative quantitative analyses, that is, bringing together different tools and techniques to provide maximum understanding, may be an approach in operationalizing clinical staging and the use of biomarkers. Overlapping the AT(N) biomarker staging nomenclature with the three-category syndromal staging of AD (Figure 2) illustrates how combinations may influence our understanding of a subject's position on the AD continuum. In addition to the ability to identify amyloid-positive and tau-positive subjects, combination biomarkers offer additional value in reducing the sample size required to detect reduced cognitive decline in response to an investigational therapy.

4 | NEURODEGENERATION

In the AT(N) framework, "(N)," or neurodegeneration, refers not to a single entity but to multiple processes represented by the progressive loss of structure or function of neurons. In AD, neurodegeneration is not believed to be due to an initiating event in the underlying pathophysiology of the disease but, rather, to a "downstream" cascade of amyloid and tau accumulation; inflammation; and, particularly at older ages, other pathology. Total tau and neurodegeneration are not AD specific but also occur in normal aging and other neurodegenerative diseases. The amount of tau and neurodegeneration tracks with the degree of cognitive impairment, unlike amyloid accumulation, which begins early in the disease process, and much time passes between the onset of amyloid positivity and the manifestation of clinical effects. Longitudinal biomarker data from cognitively normal individuals across several cohorts revealed that abnormal neurodegeneration together

with amyloid and tau was linked to more progressive AD, even among people who were considered cognitively normal, at least at baseline.[41]

In the NIA-AA criteria, the primary fluid biomarker of neurodegeneration has been CSF total tau, but, more recently, neurofilament light chain (NfL) is proving useful as well. It is a molecule reflecting downstream effects and not the directly targeted biology of AD pathological changes. Moreover, it can be well measured in plasma/serum and, thus, is suitable for monitoring purposes and has become the most widely used marker of neurodegeneration. NfL is a validated, analytically and preanalytically robust, cross-disease marker of neurodegeneration and may be useful for stratification and monitoring in stage 1 and 2 AD trials. CSF NfL has been a robust biomarker of a plethora of neurological diseases, such as Huntington's, Parkinson's, amyotrophic lateral sclerosis, and for treatment effectiveness in multiple sclerosis. Now, ultrasensitive technology allows for NfL to be detectable in blood, which offers versatility in clinical trials and serial measurements. In the Dominantly Inherited Alzheimer Network (DIAN) cohort, both CSF NfL and serum NfL began increasing very early—onset about −10 years—which is a similar timeframe for the onset of amyloid and tau changes.[42] Future research will be needed to isolate the etiology of neurodegeneration in the context of multiple coexisting pathologies. Looking at subtle differences in relationships between these biomarkers will be critical for this future work.

As neurodegenerative-marker measurements are not strongly correlated, likely reflecting different pathological mechanisms that result in neurodegeneration, one must be careful in interpreting agreement between biomarkers of neurodegeneration in cognitively unimpaired groups in whom, by definition, dynamic range is limited. Whether neurodegeneration biomarkers are adequately interchangeable for a clinical trial is a study-specific issue. Despite the challenges of defining positive and negative status for neurodegeneration, abnormal neurodegeneration markers at baseline in conjunction with amyloid and tau can be used to identify people likely to decline during a clinical trial. Some researchers believe the most utilitarian N marker is magnetic resonance imaging (MRI) because it is essential for inclusion purposes in any AD trial that administers an intervention that affects the brain—because trialists need to know at baseline the status of each participant's brain. A welcomed algorithm would be one that defines the degree of neurodegeneration, based on MRI, expected for a given load of core pathology—amyloid and tau pathology. Potential trial enrollees then could be screened out if their degree of neurodegeneration exceeded their predicted load. As outcome measures, N markers could be particularly useful to assess global, nonspecific neuronal injury in intervention trials involving multiple targets or having multiple mechanisms.

Biomarkers have the potential to improve design for secondary prevention trials. They are necessary to identify individuals in stages 1 and 2 AD through brain health registries. Using biomarkers increases screen failure rates but decreases heterogeneity and can increase the chances a therapeutic can demonstrate an effect, as biomarkers ensure the participants have the pathophysiology being targeted. Combinations of plasma markers for amyloid, tau, and neurodegeneration may be used to enrich for cognitively unimpaired individuals with high risk of future cognitive decline in preclinical AD drug trials.[43] Algorithms incorporating several non-invasive biomarkers can be used to identify amyloid and tau status, making possible personalized medicine approaches for diagnosis and prediction of subsequent cognitive decline at preclinical disease stages. This could be useful in clinical practice to help guide treatment decision when disease-modifying treatments become approved for preclinical AD. But algorithms must be evaluated systematically for combinations of plasma markers with other modalities (e.g., digital biomarkers, genetics, CSF, imaging) and need to consider scalability and cost versus performance. At this time, they have been constrained to research and educational settings, which is appropriate. They appear promising and would be extremely useful in randomized clinical trials, especially in the early preclinical stage

Amyloid remains an important index and, from the imaging perspective, correlates most closely with pathology. Although plasma amyloid markers do not yet offer the dynamic range as the plasma p-tau markers, each individually, as well as the combination, holds some promise. The possibility of biofluid markers somewhat "mediating" between amyloid PET positivity and tau PET positivity—if tau PET positivity is detecting tangles—is an intriguing notion.

5 | CLINICAL TRIALS IN AD

Researchers reason that if there are clinical benefits in removing amyloid at the symptomatic stage, the benefits should be greater if amyloid is "attacked" before downstream damage ensues. Therapeutics that can stave off cognitive decline, tau tangle accumulation, atrophy, and subsequent irreversible brain damage would be appreciably welcomed. Preclinical AD early treatment (secondary) studies in amyloid-positive, cognitively normal AD populations are collecting such data.

The AHEAD 3–45 Study is a 4-year, two-trial platform that tailors dosing regimens of an anti-amyloid monoclonal antibody to individuals with elevated baseline PET amyloid levels. The A45 arm, a phase 3 study, includes individuals with elevated amyloid levels (> 40 Centiloids) with the Preclinical Alzheimer's Cognitive Composite (PACC5) as the primary outcome; the A3 arm, a phase 2 trial, includes individuals with intermediate amyloid levels (20 to 40 Centiloids) with amyloid PET change as the primary outcome and tau PET change as a key secondary outcome. Note that A3 is the first *early* preclinical, or *pre*-preclinical AD trial.

The AHEAD Study is focused on answering whether drug effects may be measured at such an early stage of AD. Donohue et al.[44] showed that when entirely clinically normal individuals were separated on the basis of elevated and non-elevated amyloid, those with elevated amyloid steadily declined in cognition compared to individuals who had no evidence of elevated amyloid. Similarly, both ADNI and HABS confirmed that the PACC has been a reliable primary outcome measure in presymptomatic trials. [44–45]

The EARLY trial tested atabecestat, an enzyme that inhibits cleavage of the amyloid precursor protein (APP); cleavage of APP is essential in the generation of Aβ. This originally planned 4.5 year study in preclinical AD individuals with or without subjective cognitive

complaints was truncated after 3 years due to elevated liver enzymes in participants receiving atabecestat. Preliminary analyses suggested dose-related cognitive worsening and neuropsychiatric adverse events occurred,[46] and final analyses confirmed these findings.[47] The EARLY trial included both stage 1 and stage 2 preclinical AD participants. The EARLY researchers noted that whereas the NIA-AA stage 2 AD criteria mandate longitudinal cognitive decline to define preclinical stage 2 AD, the FDA's stage 2 criteria does not, and operationalizing with a single cross-sectional time point and cutoff on a sensitive neuropsychological measure is not prudent.

The Alzheimer's Prevention Initiative (API) Generation Program was comprised of two clinical trials: Generation Study 1 (GS1) examined umibecestat (an APP-cleaving enzyme inhibitor) and CAD106, an active immunotherapy; Generation Study 2 (GS2) examined umibecestat.[48] This trial program was terminated early, before recruitment was completed, due to cognitive worsening in participants taking umibecestat. To determine whether AD stages 1 and 2 could be differentiated retrospectively, the researchers examined data from the amyloid-screened population. Objective and subjective measures of cognition (Mini-Mental State Examination, Repeatable Battery for the Assessment of Neuropsychological Status, the API Composite Cognitive Test,[49] and Everyday Cognition [ECog]) did not relate cross-sectionally to amyloid or tau levels. Examining the participants with Clinical Dementia Rating global 0.5, although overall these participants had slightly more subjective concerns (as measured by ECog), there were no differences by amyloid status. They concluded that while differentiating between AD stages 1 and 2 may be possible in other, longitudinal cohorts, operationalizing stage 2 AD is not feasible with the cognitive measures used in the Generation Program.

6 | CONCLUSION

Biomarkers provide new opportunities to help characterize those in the early stages of AD. The discussions during the Spring 2021 AARR suggest it is possible to differentiate on a clinical basis individuals who may be at a stage of progressing more rapidly. The performance of plasma biomarkers Aβ42/40 and p-tau have the potential to enable broad population screening for subjects with biofluid-biomarker evidence of AD pathology. Using only biomarker-positive subjects will enable enhanced research and development of novel tools for cognitive testing and for tracking initial phases of decline in early-stage AD. The performance of blood biomarkers Aβ42/40 and p-tau have the potential for use in clinical trial enrollment and will improve the efficiency of early-stage AD clinical trials. Furthermore, the combination of SCD, objective decline, and neurobehavioral symptoms could characterize and signal which individuals may be more likely to progress, and therefore be potential candidates for treatment. Combining those clinical characteristics with biomarkers has demonstrated evidence of improved prediction of decline[50] and offers the opportunity for future research. This may also provide evidence of the substrate pathology toward which the therapeutic is targeted, with obvious potential for improving therapeutic benefit, and from an ethical standpoint may eliminate patients who do not have the target pathology and are unlikely to benefit.

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CONFLICT OF INTEREST STATEMENT

CJW and MCC are full-time employees of the Alzheimer's Association. AG is a full-time employee at Novartis. RCP is a full-time employee of the Mayo Foundation for Education and Research. CB and CR are full-time employees at WCG Clinical Endpoint Solutions. SDS a full-time employee of Eisai. HF is a full-time employee of AbbVie. JL is a full-time employee of Biogen. MP is a full-time employee of Eli Lilly. KS is a full-time employee of Genentech. Author disclosures are available in the supporting information.

CONSENT STATEMENT

As there was no experimentation with human subjects as part of this manuscript, no consent was obtained (or necessary).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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