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PERSPECTIVE

Application of the revised criteria for diagnosis and staging of Alzheimer's disease: Drug development and clinical practice

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Abstract

The newly proposed revised criteria for diagnosis and staging of Alzheimer's disease (AD) by the Alzheimer's Association (AA) Workgroup represent a significant milestone in the field. These criteria offer objective measures for diagnosing and staging biological AD, bridging the gap between research and clinical care. Although implementation feasibility may vary across regions and settings, improving the availability and accuracy of biomarkers, especially plasma biomarkers, is expected to enhance the applicability of these criteria in clinical practice. The Fall 2023 Alzheimer's Association Research Roundtable (AARR) meeting served as a forum for gathering industry perspectives and feedback on these revised criteria, ensuring that the new criteria inform research, clinical trial design, and clinical care. In this article, we outline a summary of the newly proposed "Revised Criteria for Diagnosis and Staging of AD: AA Workgroup" and provide highlights from the AARR meeting in fall 2023.

KEYWORDS
Alzheimer's disease biomarkers, Alzheimer's disease diagnosis, Alzheimer's disease imaging, Alzheimer's disease staging, Alzheimer's disease, amyloid positron emission tomography, biofluid biomarkers, preclinical Alzheimer's disease–

Highlights

- The Alzheimer's Association Research Roundtable (AARR) convened leaders from industry, academia, and government, to review the *Revised Criteria for Diagnosis and Staging of AD: AA Workgroup*, and gather industry perspectives and feedback on these revised criteria before its publication.
- The newly proposed revised criteria for diagnosis and staging of Alzheimer's disease (AD) by the AA's Workgroup represent a significant milestone, offering objective measures for the biological and staging of AD and bridging the gap between research and clinical care.

- Improving the availability and accuracy of biomarkers, especially blood-based biomarkers (BBMs) is expected to improve clinical research and enhance the applicability of these criteria in clinical practice.

1 | INTRODUCTION

Over the past decade, concerted efforts from the National Institute on Aging (NIA) and the Alzheimer's Association have shaped diagnostic criteria and research frameworks for the diagnosis and staging of Alzheimer's disease (AD) across its continuum. In 2011, three workgroups convened by the NIA–AA published separate recommendations for the diagnosis and staging of AD in its preclinical,[1] mild cognitive impairment (MCI),[2] and dementia[3] stages. These recommendations as a whole presented AD as a clinical–biomarker construct and laid the foundation for a biologically informed understanding of AD across its continuum (although the preclinical criteria defined the disease based on biomarkers alone). Following the introduction of the amyloid, tau, neurodegeneration (ATN) construct in 2016,[4] the NIA–AA took a significant step forward in 2018 by publishing a research framework that incorporated the ATN construct and operationalized biomarkers for diagnosis and staging of AD across its entire continuum.[5] The 2018 research framework emphasized the dynamic nature of the field, noting the need for future updates in response to scientific advances.

Fast forward to 2022, the Alzheimer's Association convened a workgroup to lead the revision of the NIA–AA's 2011 diagnostic criteria and the 2018 research framework. This revision aimed to incorporate recent advances in treatments[6–9] and biomarker development,[10–12] as well as a shift in the scientific community to define AD biologically rather than based on its syndromic presentation.[13] The workgroup's collaborative effort resulted in the recently published "Revised Criteria for Diagnosis and Staging of AD: Alzheimer's Association Workgroup."[14] Drafts of these criteria were posted for public comment and presented at the fall 2023 Alzheimer's Association Research Roundtable (AARR) meeting. Specifically, the fall 2023 AARR meeting served as a forum for gathering industry perspectives and feedback on these revised criteria before its publication, ensuring that the new criteria inform research, clinical trial design, and clinical care. The meeting addressed these topics with a diverse array of leaders in the field, including scientific leaders from the AARR membership, academia, the National Institutes of Health (NIH), U.S. Food and Drug Administration (FDA), and other global government agencies. This article provides a summary of key discussions at the fall 2023 AARR meeting, offering insights into the latest advancements in AD diagnosis and staging criteria.

1.1 | Summary of the Revised Criteria for Diagnosis and Staging of AD: AA Workgroup

Three major developments in the field drove the Revised Criteria for Diagnosis and Staging of AD[14] since the publication of the 2018 research framework: (1) the advent of novel FDA-approved AD therapies that target the core disease pathology[7,8] and (2) the emergence of increasingly more accurate blood-based biomarkers (BBMs) for AD that hold the promise of enhancing the accessibility of AD diagnosis both for research and clinical care.[10,11,15] The third development was the recognition that although imaging and biofluid biomarkers within a category were often concordant they were sometimes not, and this required reorganizing biomarker categorization from the 2018 framework.

These revised criteria retain key principles from the NIA–AA's 2018 research framework[5] and the 2011 preclinical recommendation,[1] defining AD as a biological process that begins with the appearance of detectable pathological changes before symptom onset. However, it has transitioned beyond an exclusive research framework to criteria that aim to inform both research and clinical care. It is important to note that the Revised Criteria do not offer step-by-step guidance on clinical workflow or treatment protocols. Instead, they underscore the role of clinicians and that the biological diagnosis of AD is meant to assist rather than supplant clinical evaluation in individuals with cognitive impairment.

1.2 | Biomarker categorization

In the Revised Criteria, biomarkers are categorized into three main categories:

1. Core biomarkers of AD neuropathologic changes that are specific to AD and are differentiated by the timing of abnormality onset and intended use:
   a. Core 1 includes biomarkers of the amyloid beta (Aβ) proteinopathy pathway (**A**) and biofluid biomarkers of phosphorylated and secreted AD tau ($\mathbf{T_1}$) which become abnormal early in the disease process around the time that abnormality is apparent on amyloid positron emission tomography (PET).
   b. Core 2 are biomarkers of AD tau proteinopathy ($\mathbf{T_2}$) that become abnormal later in the disease process (e.g., neurofibrillary tangle pathology).
2. Biomarkers of nonspecific processes involved in AD pathophysiology:
   a. Injury, dysfunction, or degeneration of neuropil (**N**)
   b. Inflammation or immune mechanisms (**I**)
3. Biomarkers of non-AD co-pathologies:
   a. Vascular brain injury (**V**)
   b. α-Synuclein (**S**)

Overall, core biomarkers are those involved in the A (Aβ) and T (tau) proteniopathy categories. An abnormal Core 1 biomarker alone can

diagnose AD and guide clinical decisions. Core 2 biomarkers, however, are typically not used as standalone tests for AD diagnosis; but, when paired with Core 1, they enable staging the severity of the biological disease and offer prognostic insights.

2 | DIAGNOSIS

The diagnosis of AD can be established by an abnormality on specific Core 1 biomarkers, including amyloid PET; cerebrospinal fluid (CSF) Aβ42/40, CSF phosphorylated tau (p-tau)181/Aβ42, CSF total tau (t-tau)/Aβ42; or "accurate" plasma assays. The revised criteria set rigorous minimum diagnostic accuracy requirements for biomarkers, particularly in reference to BBMs (e.g., plasma p-tau217). The minimum requirement is an accuracy of 90% for the identification of moderate/frequent neuritic plaques at autopsy (or an approved surrogate, which at this point would be amyloid PET or approved CSF assays) in the intended-use population. For BBMs, this translates to an accuracy equivalent to that of approved CSF assays.

The revised criteria further emphasize that in the absence of approved treatments for asymptomatic individuals, AD biomarker testing is not recommended in this population outside the context of observational or therapeutic research studies. However, this could change in the future if therapeutic interventions are shown to be beneficial and are approved by regulators for this population.

3 | STAGING

The revised criteria propose separate biological and clinical staging systems. The biological staging is a four-point scale (A–D) based on the ordering of events in the natural history of the disease. It can be accomplished by a combination of amyloid and tau PET or a combination of Core 1 biofluid and tau PET. A forward-looking conceptual staging approach based only on biofluid biomarkers is also proposed.[16,17]

The clinical staging adopts a six-point numeric scale ranging from asymptomatic (Stage 1) to severe dementia (Stage 6).[5] Stages 1–6 are applicable only to individuals with biomarker evidence of AD. In addition, the revised criteria propose the addition of "Stage 0," which is defined as genetically determined AD (autosomal dominant AD and Down syndrome AD)[18] in a clinically asymptomatic individual with negative biomarker results.

An integrated biological and clinical staging is also proposed to convey the interconnected nature of the biological and clinical staging of AD.[19] However, factors that could contribute to a common mismatch between clinical and biological stages are acknowledged by emphasizing the modifying influence of common co-pathologies (such as neuronal α-synuclein disease, TAR DNA-binding protein 43 (TDP-43), and cerebrovascular disease), cognitive reserve, and resistance.

3.1 | Limitations of biomarkers

One limitation of the existing biomarkers is the lack of thoroughly studied biomarkers for all relevant AD co-pathologies, such as Limbic-predominant age-related TDP-43 encephalopathy (LATE) and vascular brain injury (where an accepted comprehensive metric does not yet exist). Consequently, determining the proportion of cognitive deficits attributable specifically to AD versus other neuropathological conditions remains uncertain. Such limitations underscore the importance of clinical judgment when implementing the revised criteria clinically. Other limitations of currently available AD biomarkers are the lack of certified biofluid reference methods and materials (except for CSF Aβ42 and Aβ40)[20,21] and that PET, CSF, and blood biomarkers are less sensitive than neuropathologic examination for detecting early/mild AD neuropathologic changes. However, their lower sensitivity could also be viewed as a strength because Core 1 biomarkers indicate the likely presence of both plaques and tangles. The latter is a key point because a common misunderstanding is that the revised criteria base a diagnosis of AD on the presence of amyloid plaques alone. Core 1 biomarkers denote the presence of both plaques and tangles.

4 | BIOMARKERS: PERFORMANCE AND CONTEXT OF USE

4.1 | Defining performance criteria and accuracy standards for PET biomarkers

The regulatory approval of amyloid and tau PET ligands has been based on visual reads. The visual readings of FDA-approved amyloid-PET scans have demonstrated high accuracy with respect to a neuropathologic reference standard.[22–24] For example, visual reads of florbetapir PET imaging have shown a sensitivity of 92% and specificity of 100% in detecting CERAD (Consortium to Establish a Registry for Alzheimer's Disease) moderate to frequent plaques in individuals who had an autopsy within 2 years of imaging.[22] Although visual reads are highly accurate in clinical trial settings, little is known about their accuracy in real-world clinical settings. To address this question, a subset of amyloid-PET scans performed within the IDEAS (Imaging Dementia – Evidence for Amyloid Scanning) study were compared for visual reads between community physicians and panels of three expert readers. The results demonstrated excellent agreement between the expert read and local reads, suggesting the high reliability of visual amyloid-PET scans in real-world clinical settings.[25]

Although the FDA approval of PET ligands was based primarily on visual reads, the field is moving toward greater use of quantitative methods. In this context, the Centiloid (CL) scale has emerged as a promising method for the quantitative assessment of amyloid-PET scans. The reliability and feasibility of the CL method have been demonstrated in a multi-center study by showing a positive correlation with CERAD neuritic plaque scores and Thal Aβ phases.[26] Furthermore, their result suggests that a positive amyloid PET scan based on CL thresholds is indicative of intermediate to high AD neuropathology and that it captures both amyloid and tau pathology. Real-world applications further confirm the reliability of the CL method, showing substantial concordance with visual reads of amyloid PET scans.[27]

Regarding tau PET, the discussions at the meeting highlighted the importance of considering the medial temporal lobe, as its inclusion can significantly enhance sensitivity at earlier disease stages. Regulatory approval of Tauvid has been based on studies comparing PET scans to autopsy results, with a specific emphasis on detecting advanced pathology (Braak Stages V/VI).[28] However, there is a need for more-sensitive measures to capture the tau burden at earlier stages of the disease. The inclusion of the medial temporal lobe has been shown to increase the sensitivity of Tauvid for Braak III/IV stages.[29] Moving forward, ongoing research endeavors like the CenTaur project are dedicated to standardizing tau PET quantification methodologies. These initiatives aim to tackle the challenges posed by the variability among tau PET tracers and the absence of a universally accepted gold standard tracer.

4.2 | Defining performance criteria and accuracy standards for BBMs

In recent years, one of the most significant advancements in AD diagnostics has been the development of BBMs, which are projected to revolutionize clinical care and research with some but not all BBM assays exhibiting accurate diagnostic performance.[10,11] Head-to-head comparison of several plasma p-tau assays supports the superior performance of mass spectrometry–based p-tau217 measurement to detect abnormal Aβ status and progression to AD in patients with MCI.[15] In addition, p-tau immunoassays, particularly p-tau217, have been shown to perform relatively consistently in relation to both outcomes.[10] Recently, a study comparing the performance of plasma %p-tau217 (ratio of p-tau217 to non-p-tau 217) and CSF tests in detecting AD pathology by PET showed that plasma %p-tau217 is similar or superior to clinical CSF tests.[30] Specifically, the study showed that among patients with MCI and mild dementia, plasma %p-tau217 was clinically equivalent to CSF tests in classifying Aβ PET status, and outperformed CSF tests in classifying tau pathology.[30] In other studies, BBMs have also been compared with their neuropathologic correlates, showing that high-performing assays of plasma p-tau217 and Aβ42/40 are promising optimal combinations for assessing AD-related pathology in vivo.[31]

The emergence of disease-modifying therapies for early AD has heightened the need for rapid and accessible diagnostic tools. In this context, BBMs offer a less invasive and potentially cheaper alternative to gold-standard PET and CSF biomarkers. The Global CEO Initiative on Alzheimer's Disease (CEOi) defined minimum performance criteria for BBMs for clinical use in symptomatic individuals, considering both triaging (initial BBM test with the plan for a confirmatory test if positive) and confirmatory (BBM test without a subsequent test) contexts of use.[32] For triaging, it was found that BBMs should achieve ≥90% sensitivity and ≥85% specificity, slightly lower than CSF tests. For confirmation of amyloid pathology, it was found that BBMs should match CSF tests' performance with ≥90% sensitivity and ≥90% specificity.[25] In addition, BBMs should exhibit less than 5% discordance in repeated testing within a short interval. High-performance BBMs, possibly using a two-cutpoint approach to establish normal, abnormal, and intermediate values, have the potential to meet these standards and enable potential broader access to accurate diagnosis of AD.[33] Moreover, the stability of biomarker measurements over time, reflected in test–retest variability, is critical for clinical utility.[11,34] Finally, it is important to note the interpretation of test results depends on the prevalence of amyloid pathology in the population (pre-test probability).

4.3 | Real-world use of biomarkers to determine amyloid status in a memory clinic

The FDA approval of anti-amyloid therapies for AD has significantly changed the utilization of AD biomarker testing in clinical practice. Before the FDA approval of anti-amyloid therapies, biomarker testing was infrequent and was reserved primarily for cases with diagnostic uncertainty.[35] Notably, individuals with a high clinical suspicion of AD often did not undergo biomarker testing under the assumption that positive results would not significantly change management strategies. However, with the FDA's approval of lecanemab and donanemab,[7,8,36,37] and the subsequent Centers for Medicare & Medicaid Services (CMS) decision to cover lecanemab,[38] confirmation of amyloid positivity to determine eligibility for anti-amyloid therapies has emerged as the foremost reason for conducting biomarker tests.[39] The initiation of anti-amyloid therapies requires biomarker confirmation of elevated amyloid levels, thus making biomarker testing a crucial step in the evaluation of patients being considered for anti-amyloid therapies.

Given the high costs and the specialized equipment and personnel needed for PET imaging, many specialty clinics predominantly utilize CSF testing for assessing amyloid status. However, lumbar puncture is inadequately reimbursed, which may reduce the availability of this modality at many memory clinics and present a barrier to accessing FDA-approved anti-amyloid therapies.[40] Furthermore, limited knowledge about the interpretation of CSF tests may lead to incorrect conclusions. For example, although the ratios of p-tau181/Aβ42 or t-tau/Aβ42 are the FDA-approved CSF measures for determining amyloid status,[41] some clinicians may interpret amyloid status based on CSF Aβ42 concentrations alone, potentially leading to inaccurate diagnoses. Overall, it is imperative to employ biomarker tests that are aligned closely with gold standard reference measures and to avoid or exercise caution with biomarkers that have lower associations with reference measures.

4.4 | Concordance of AD biomarkers

Leveraging data from Alzheimer's Disease Neuroimaging Initiative (ADNI), a study by Eli Lilly[42] found that clinically available CSF tests (Lumipulse Aβ42/40 & Elecsys P-tau181/ Aβ42) are highly concordant with amyloid-PET visual reads, consistent with previous research.[43,44] It was also demonstrated that CSF tests were noninferior[45] to amyloid-PET for identifying patients with AD pathology who may be suitable for treatment with AD-modifying therapies. Furthermore, a high negative

predictive value (NPV; 98.1%) was observed between CSF assays and tau PET visual read; however, the positive predictive value (PPV) was 64.0%. It was noted that an alternative threshold derived against a tau-PET reference standard may improve concordance of CSF assays with tau PET. In addition, better concordance of CSF assays with an earlier, temporal tau-PET region[29] was observed (NPV 94.2%; PPV 81.3%); this supports the meeting discussions outlined in Section 3.1, suggesting that temporal or medial-temporal tau PET evaluations may be more sensitive at an earlier disease stage.

Although tau-PET visual read may not be optimized for the very early identification of AD, data from Lilly Study A05 demonstrated that a positive tau-PET visual read accurately identifies patients also positively identified by amyloid-PET (PPV 96.7%), supportive of an AD diagnosis[46]; similar results were reported by Hammes.[47]

An evaluation of data from BioHermes demonstrated that a clinically available Aβ42/40 plasma test (C2N, Precivity AD) was able to identify patients selected by amyloid PET but was less effective in ruling out patients, similar to the A4 study results.[48] New plasma diagnostics that incorporated p-tau217 had a higher agreement with amyloid-PET imaging.[49] Similar to the CSF tests, it was also demonstrated that both plasma Aβ42/40 and p-tau217 biomarkers were noninferior to amyloid-PET for identifying patients with AD pathology. It should be noted that these evaluations consider concordance as part of the natural history of disease and have not evaluated the efficacy of CSF or plasma biomarkers to identify treatment-related amyloid clearance (TRAC).

Overall, these results suggest that CSF and plasma assays of Aβ and p-tau are useful for supporting an AD diagnosis, and identifying patients with AD pathology who may be suitable for treatment with AD-modifying therapies. The adoption of CSF, and especially BBMs would enable more equitable access to diagnosis and ultimately disease-modifying therapies in AD. The complex and changing relationships between biomarkers over the course of the disease and how such biomarkers are implemented are critical factors that need further consideration as the field progresses.

4.5 | Feasibility and scalability of biomarkers for early detection in AD

Although FDA-approved PET and CSF biomarker tests can accurately assess AD pathology, their limited clinical implementation due to availability, cost, and perceived invasiveness hinders feasibility and scalability. In contrast, BBMs hold promise for earlier, faster diagnoses and for aiding in risk assessment, prognosis, and management. Validation studies for BBMs, especially for plasma p-tau217 and the recently completed study comparing various p-tau217 and p-tau181 assays across time and with comparisons to amyloid-PET and tau-PET measures, strongly support the selection of p-tau217 as a leading plasma biomarker test for reliable detection of amyloid pathology.[50–52] However, additional research is needed across diverse populations to ensure real-world applicability. Moreover, robust biomarkers for other important physiological processes and pathologies involved in AD, such as inflammation, dementia with Lewy bodies (DLB), and TDP-43 pathologies, remain needed. Recent studies using the α-synuclein seed amplification assay in patients with AD demonstrated promising results for the detection of pathologic synuclein in several study cohorts, providing promise that detection of this common co-pathology will be feasible in future trials and hopefully in clinical practice in the future.[12,53]

Future research should focus on enhancing the feasibility and scalability of plasma AD testing across diverse populations. This includes finalizing preanalytics and ensuring robust assays with a 90% sensitivity/specificity across multiple study populations using amyloid-PET and neuropathologic-based studies as the standard of truth. The planned development of certified reference material for p-tau217 under the auspices of the International Federation for Clinical Chemistry (IFCC), as was done for CSF Aβ42 and Aβ40, will provide additional strong support for the ultimate standardization of this leading contender for widespread use as an effective plasma-based test for amyloid pathology. Furthermore, establishing cut-points and context of use across populations and achieving external QC performance with multicenter studies to ideally reach a 5%–10% coefficient of variance are crucial steps forward.

4.6 | Neuronal synuclein disease: A biological definition and integrated staging system

The Fall 2023 AARR meeting also delved into discussions about the newly proposed biological definition of neuronal α-synuclein disease (NSD), which unifies Parkinson's disease (PD) and DLB,[54] drawing parallels with other neurodegenerative disorders such as AD and Huntington's disease.[5,55] Given recent biomarker advancements, particularly the α-synuclein seed amplification assay enabling accurate detection of pathological α-synuclein in CSF, a conceptual shift has been proposed, suggesting a unifying biological definition of PD and DLB termed NSD. This biological concept is a major shift in redefining PD and DLB based on their biology rather than clinical symptoms.[54]

NSD is defined by the presence of pathological neuronal α-synuclein species detected in vivo, irrespective of specific clinical syndromes. Accordingly, individuals with pathological neuronal α-synuclein are proposed to be at increased risk of dopaminergic neuronal dysfunction. Based on this, the NSD Integrated Staging System (NSD-ISS) is introduced as a structured approach to categorizing disease progression based on the biological anchors and the degree of functional impairment caused by clinical symptoms.[54]

The significance of the NSD-ISS concept lies in its potential to accelerate therapeutic development at all disease stages, from before symptom onset through mild to severe functional impairment, and offer a research framework within which to answer key outstanding research questions. Furthermore, the NSD-ISS concept is expected to reduce heterogeneity in clinical trials and provide a framework for clinical trial design and evaluation by key constituencies.[54]

An example of therapeutics targeting early-stage NSD is the "Path to Prevention" (P2P) platform nested within the Parkinson's Progression

Marker Initiative (PPMI). The P2P platform is designed to evaluate the safety and early efficacy of investigational products for the treatment of early-stage NSD. Leveraging PPMI resources, the P2P platform focuses on recruiting individuals in Stage 2B of the NSD-ISS. These individuals are α-synuclein positive, have dopamine transporter (DAT) deficit, and present a clinical phenotype defined as clinically detectable premotor or subtle motor abnormalities without functional impairment. Overall, trials such as P2P are made possible by advancements in biomarkers and the biological definition of NSD, presenting a unique opportunity to conduct interventional trials at early disease stages with the potential of preventing or halting the disease progression.

5 | IMPLEMENTATION AND FUTURE DIRECTIONS

5.1 | Patient enrichment and impact on inclusion/exclusion criteria in symptomatic individuals in AD clinical trials

Over the past decade, the ATN framework has significantly impacted the design and enrollments of AD clinical trials, particularly in the context of earlier-stage interventions. Historically, AD clinical trials have relied on clinical symptomatology for participant enrollment, inadvertently including individuals who lack the underlying AD pathology. However, the introduction of a biological basis for diagnosis and staging of AD has revolutionized AD clinical trial methodologies. This shift has enabled the identification of individuals who are more likely to respond to anti-amyloid treatments while reducing biological heterogeneity, albeit frequent concurrent pathologies such as, for example, a vascular component, cannot entirely be excluded yet. Notably, the ATN framework has served as the basis for participant inclusion in two recent positive Phase 3 trials in early AD: the Clarity trial of lecanemab and the Trailblazer-ALZ 2 study of donnemab.[7,8] Both trials selected participants based on the ATN criteria, including amyloid PET, tau PET, or CSF, in addition to clinical criteria. The primary outcomes of both trials showed significant slowing of disease progression, particularly in earlier disease stages in those with lower baseline tau levels. Together, these landmark AD clinical trials have opened up a new landscape in AD treatment and diagnosis.

5.2 | Conducting clinical trials in asymptomatic individuals with positive biomarkers

The field of AD clinical trials is moving toward primary prevention (preventing the onset of AD pathology) by developing interventions in the early AD stages, when pathological changes associated with AD are present in the brain but cognitive and functional decline are not yet present (preclinical). The A4 study has previously shown no evidence of a beneficial clinical effect with an anti-amyloid antibody targeting monomeric forms of Aβ in preclinical AD.[56] However, the study showed that baseline amyloid PET and plasma p-tau217 have a strong association with the rate of cognitive decline and risk of progression to functional impairment. Furthermore, in a study supported by the Alzheimer's Association, Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) participants who did not have elevated amyloid at baseline did not demonstrate cognitive decline over the follow-up period. Overall, these results are supportive of the hypothesis that targeting soluble monomeric Aβ alone does not remove plaques, and that plaque removal is associated with a beneficial effect on the rate of cognitive decline. In this context, ongoing forward-looking trials such as the Trailblazer-ALZ 3 and AHEAD 3-45 explore the safety and efficacy of anti-amyloid treatments in preclinical AD while utilizing plasma biomarkers for participant screening and selection.

A key question in designing clinical trials for preclinical AD revolves around the optimal identification of cognitively unimpaired individuals with AD who are more likely to undergo disease progression. Recently, the AHEAD 3-45 study has shown that incorporating BBMs such as %p-tau217 along with Aβ42/Aβ40 into screening algorithms may streamline screening preclinical individuals into anti-amyloid clinical trials.[57] Ultimately, such biomarkers may also need to be employed as primary outcomes in clinical trials examining various interventions to move the field closer toward the development of primary prevention for AD.

5.3 | Targeting tau pathology

Beyond anti-amyloid therapies targeting aggregated Aβ species, one of the most active areas of AD clinical development is tau therapies. As of December 2023, at least 19 anti-tau therapies are in clinical development.[58] This momentum is fueled by advancements in tau biomarkers, facilitating a deeper understanding of tau pathophysiology dynamics and their relationship to clinical progression, as stipulated neuropathologically by Braak and Braak in 1991.[59] In this landscape, ongoing trials at the Alzheimer's Clinical Trials Consortium (ACTC), such as the Alzheimer's Tau Platform, are aimed at studying multiple tau drugs alone and in combination with amyloid removal in preclinical AD. Other notable trials targeting tau pathology are the TANGO trial (a placebo-controlled randomized phase 2 study of efficacy and safety of the anti-tau monoclonal antibody gosuranemab in early AD)[60] and a multiple-ascending dose (MAD) study of BIIB080.

Exploratory analysis of tau biomarker data in the TANGO study showed a moderate correlation between plasma p-tau181 levels and both amyloid and tau pathology, suggesting an unmet need for plasma tau biomarkers that specifically capture tau pathology.[60] Furthermore, longitudinal analyses of TANGO data showed that placebo-treated participants with greater change in plasma p-tau181 levels over 18 months progressed more rapidly across clinical endpoints. These exploratory data highlight the potential efficacy of incorporating longitudinal biomarker data into the definition of biomarker thresholds to predict clinical progression. Another promising trial targeting tau pathology is a MAD study of BIIB080, which is a promising tau-targeting molecule designed to reduce the production of all forms of tau.[61,62] Data from the BIIB080 Phase 1B study showed a reduction in

tau burden with high-dose BIIB080 treatment as demonstrated using tau-PET data.[25,62] Together, data from such trials show the potential for tau-PET surrogacy as a future endpoint in AD trials targeting tau pathology, while there remains a need for data harmonization, data sharing, and longitudinal biomarker data utilization. Larger-scale data collection and data sharing are critical to inform the best use case for tau-PET and tau fluid biomarkers.

5.4 | Plasma tests as triaging to tertiary care for treatment in primary care

Although BBM assays have shown significant promise in detecting AD pathology in research settings, their implementation in primary care settings remains largely unexplored. Real-world validation studies, including those conducted in memory clinics and primary care settings, are essential to ensure the practical applicability of BBMs. These studies should employ predefined cutoff values and encompass diverse patient populations to accurately reflect the variability encountered in clinical practice.[11]

To assess whether BBMs are ready for use in primary care, particularly for triaging purposes, the BioFINDER-Primary Care study aimed to examine the diagnostic accuracy of BBMs as compared to usual care by primary care physicians (PCPs). Over 300 patients with cognitive complaints were recruited across primary care centers in Sweden. This study showed that PCPs correctly identified AD in only 54% of cases and their diagnostic certainty was low. However, plasma p-tau217 had an accuracy of over 90% either as a standalone test or combined with Aβ42/40, indicating the promising potential of integrating plasma p-tau assays into primary care settings.[63,64] It should be noted that implementation of such tests in primary care settings requires the development of clear clinical guidelines for test interpretation.

5.5 | Operationalizing the revised criteria in clinical practice

The meeting thoroughly explored the practical implementation of the revised criteria for diagnosis and staging of AD within clinic settings, including memory clinics, emphasizing the crucial role of clinical judgment alongside biomarker test results. Treatment decisions in these clinical settings are multifaceted, considering variables such as comorbidities and individual patient characteristics in addition to biomarker data. Several case studies presented at the meeting underscored the intricate nature of AD diagnosis and treatment within memory clinics.

Although the immediate integration of the revised criteria into memory clinics remains to be fully understood, it marks a significant milestone for research endeavors, reflecting the evolving landscape of AD diagnosis and treatment. Nonetheless, several inquiries persist. Research efforts are necessary to elucidate the factors contributing to misalignment between clinical and biological staging, and validation studies are imperative to ascertain the feasibility of implementing plasma biomarkers in diverse communities and underrepresented groups.

6 | SUMMARY

AD was originally characterized as a disease associated with abnormal accumulation of amyloid plaques and neurofibrillary tangles in the brain. However, for many decades the diagnosis and staging of its severity were predominantly reliant on the presence and progression of clinical symptoms. More recently, advancements in imaging and biofluid biomarkers have highlighted the long preclinical phase of AD, during which detectable pathophysiological abnormalities precede clinical symptoms. These groundbreaking advances have led to a conceptual shift in the field, establishing AD as a biological continuum, and providing an opportunity to stage AD's pathological changes starting in the preclinical phase. The newly proposed Revised Criteria for Diagnosis and Staging of AD by the AA's Workgroup represent a significant milestone, offering objective measures for diagnosing and staging biological AD and bridging the gap between research and clinical care. Although implementation feasibility may vary across regions and settings, improving the availability and accuracy of biomarkers, especially BBMs, is expected to improve clinical research and enhance the applicability of these criteria in clinical practice.

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CONFLICT OF INTEREST STATEMENT

C.J.W. is a full-time employee of Mayo Clinic. A.G. is a full-time employee of Novartis. S.C.B., E.G.D., and P.M. are full-time employees of Eli Lilly and Company. H.J.M. is a full-time employee of Athira. E.S. is a full-time employee of Acumen Pharmaceuticals. K.M.S. is a full-time employee of Genentech. L.M.S. is a full-time employee of the University of Pittsburg. C.T.H. is a full-time employee of Novo Nordisk. S.M., C.J.W., and M.C.C. are full-time employees of the Alzheimer's Association Author disclosures are available in the Supporting Information.

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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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