March 1, 2026

ADLM/CSCC Clinical Laboratory Guidance Document on Alzheimer's Disease Biofluid Biomarkers

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Abstract

Alzheimer's disease biofluid biomarkers have transformed the diagnostic landscape, enabling detection of underlying pathology prior to the onset of severe cognitive decline. Cerebrospinal fluid (CSF) biomarkers — specifically the ratios of Aβ42/Aβ40, p-tau181/Aβ42, and t-tau/Aβ42—remain the gold standard for biofluid biomarker testing. The emergence of blood biomarkers, particularly p-tau217 assays achieving ≥90% diagnostic accuracy, marks a paradigm shift toward more accessible testing options. Current recommendations focus on diagnosis of symptomatic individuals in specialized care settings, including in the context of eligibility for anti-amyloid therapies. Implementation of Alzheimer's disease biofluid assays require careful consideration of preanalytical factors, analytical and clinical performance in intended use populations, and interpretive support for clinicians. This guidance document represents the authors' expert opinion grounded in the latest available evidence and best practices for implementing and interpreting Alzheimer’s disease biofluid biomarkers in clinical practice. This document was prepared in recognition of the rapidly evolving literature, particularly for blood biomarkers, for which ongoing advancements are expected. Future developments for both blood and CSF biomarkers include ongoing standardization efforts, expanded research into pre-clinical and primary care applications, enhanced clinician education, and development of new biomarkers for related co-pathologies to provide more comprehensive diagnostic insights.

Abbreviations

Aβ, amyloid-β peptides; Aβ40, amyloid-β peptide spanning residues 1-40; Aβ42, amyloid-β peptides spanning residues 1-42; AD, Alzheimer's disease; CRM, certified reference material; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; LP, lumbar puncture; MTBR-tau243, microtubule-binding region (MTBR) of tau containing the residue 243; NfL, neurofilament light chain; PET, positron emission tomography; p-tau, phosphorylated tau; p-tau181, tau phosphorylated at residue 181; p-tau217, tau phosphorylated at residue 217; p-tau231, tau phosphorylated at residue 231; t-tau, total tau (referring to detection of several tau proteoforms without discrimination)

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1) Introduction

Alzheimer's disease (AD) is the leading cause of dementia, with over 50 million cases worldwide (1), affecting memory, thinking, and behavior. Its hallmark neuropathological features are extracellular plaques containing aggregated amyloid-β peptides (Aβ) and intraneuronal neurofibrillary tangles containing the aggregated microtubule-associated protein tau (2). These pathological features are fundamental to the current understanding of disease pathogenesis and have driven diagnostic approaches, with Aβ aggregates serving as the primary diagnostic target for identifying AD pathology.

Historically, clinicians diagnosed AD antemortem based on clinical criteria, with confirmation requiring post-mortem neuropathological detection of amyloid plaques (3, 4). This approach shifted with the development of amyloid imaging tracers and biofluid assays for AD, biomarkers are now routinely used in patient care and are essential tools for accurate and timely antemortem diagnosis of AD (5). Brain imaging techniques using radioactive tracers, such as amyloid and tau positron emission tomography (PET), provide measures of the accumulation and overall brain burden of plaques and tangles, respectively (6). Biofluid biomarkers, measured primarily in cerebrospinal fluid (CSF) or blood, reflect biochemical changes resulting from amyloid aggregation in the brain and downstream effects on pathologies that include tau and neurodegeneration (7).

The first AD fluid biomarker candidates emerged in the 1980s after Aβ was extracted from cerebral blood vessels and plaques and biochemically sequenced, revealing that specific proteoforms could serve as disease indicators. Further studies demonstrated that various Aβ peptides are generated from the transmembrane amyloid-β precursor protein, via a series of *in vivo* proteolytic steps (8, 9). With Aβ peptides arising from the transmembrane portion of the amyloid-β precursor protein, those containing more residues normally buried in the hydrophobic lipid bilayer, especially Aβ42, aggregate more readily *in vivo* and are the predominant form found in plaques(10). Early immunoassays for Aβ peptides demonstrated that Aβ42 in CSF was decreased in persons with AD (11). While the Aβ40 concentration in CSF is not associated with AD, it has been used in a ratio with Aβ42, acting as a normalizing factor to account for biological (*in vivo*) variability in Aβ production and *in vitro* loss of Aβ peptides (12).

Similarly, a second set of AD fluid biomarker targets, tau proteoforms, emerged given the presence of hyperphosphorylated tau tangles in the brain. In AD, tau aggregates and is hyperphosphorylated at multiple phosphorylation sites and subject to other post-translational modifications (13). CSF contains multiple tau proteoforms, including post-translationally modified forms, such as hyperphosphorylation (14, 15). In AD, CSF concentrations of total-tau (t-tau) and p-tau are increased (16), a finding that fostered further developments of assays against different epitopes that improved the identification of Alzheimer’s pathology. Researchers have extensively evaluated the accuracy of PET and core CSF biomarkers for detecting AD pathology, with corresponding data on the newer blood biomarkers expanding at a rapid pace. Multiple studies have validated amyloid PET and core CSF biomarkers against the gold standard—post-mortem neuropathological findings of Aβ aggregation in brain tissue (17-20)—and against each other (21). Amyloid PET and CSF have demonstrated high concordance as well as high clinical sensitivity and specificity, typically exceeding 90% for

the detection of AD pathology. Diagnostic accuracy studies of CSF biomarkers often employ amyloid PET as a surrogate for neuropathological findings, as it facilitates the study of larger cohorts and concurrent comparisons (17-19). For AD blood biomarkers, both CSF and amyloid PET are considered reasonable surrogates for neuropathology, and thus are predominantly reported in the literature as the comparator when assessing the accuracy of blood biomarkers.

Each biomarker modality offers distinct advantages. PET offers the advantage of localization of pathology within the brain; CSF and blood have the advantages that multiple biomarkers can be determined from one sample and that biomarker changes may be detected earlier, i.e., prior to the deposition of sufficient amyloid plaques or tau tangles to be detectable via imaging (22). Longitudinal studies measuring multiple biomarkers in aging cohorts have established models describing the sequential events of AD progression. The temporal sequence of biomarker changes is illustrated in **Figure 1**. In summary, AD related changes in fluid Aβ42 biomarkers occur close-in-time or slightly before changes in amyloid PET, while changes in fluid phosphorylated tau biomarkers occur close-in-time or slightly after changes in amyloid PET and prior to changes in tau PET (23-25). A critical insight gleaned from biomarker research over the past 20 years has been a more detailed understanding of the progression of AD pathology. Pathological changes begin years to decades before the onset of clinical symptoms (23). With advances in biomarker diagnostics, AD pathology can now be detected 20 or more years before an individual becomes symptomatic (2). It is important to note however that not all individuals with evidence of AD pathology will develop symptoms during their lifetime (26). In clinical care, AD biomarkers are playing an increasingly important role in the evaluation of individuals presenting with cognitive complaints, such as distinguishing AD from other forms of dementia, confirming or excluding AD pathology even at early symptomatic stages, and assessing eligibility for disease-modifying therapies (27, 28). With the advent of pharmacotherapies that target the removal of Aβ aggregates from the brain, and clinical trials showing slowing of clinical progression (29, 30), there is now an urgent need to employ biomarkers to confirm the presence of AD pathology before prescribing treatment. Beyond access to current and emerging pharmacotherapies, accurate diagnosis of AD facilitates the development of an appropriate overall plan for treatment, care, and support (27, 28).

With the regulatory approval of several CSF and blood biofluid biomarkers for AD pathology, this document provides guidance for clinical laboratories on the implementation and use of these biofluid biomarkers. The recommendations presented herein reflect current available evidence and expert opinion based on best practices for biomarker measurement, quality assurance, result interpretation, and reporting. While the field continues to evolve rapidly, this guidance document aims to support laboratories in delivering accurate and reliable AD biomarker testing to support clinical decision-making.

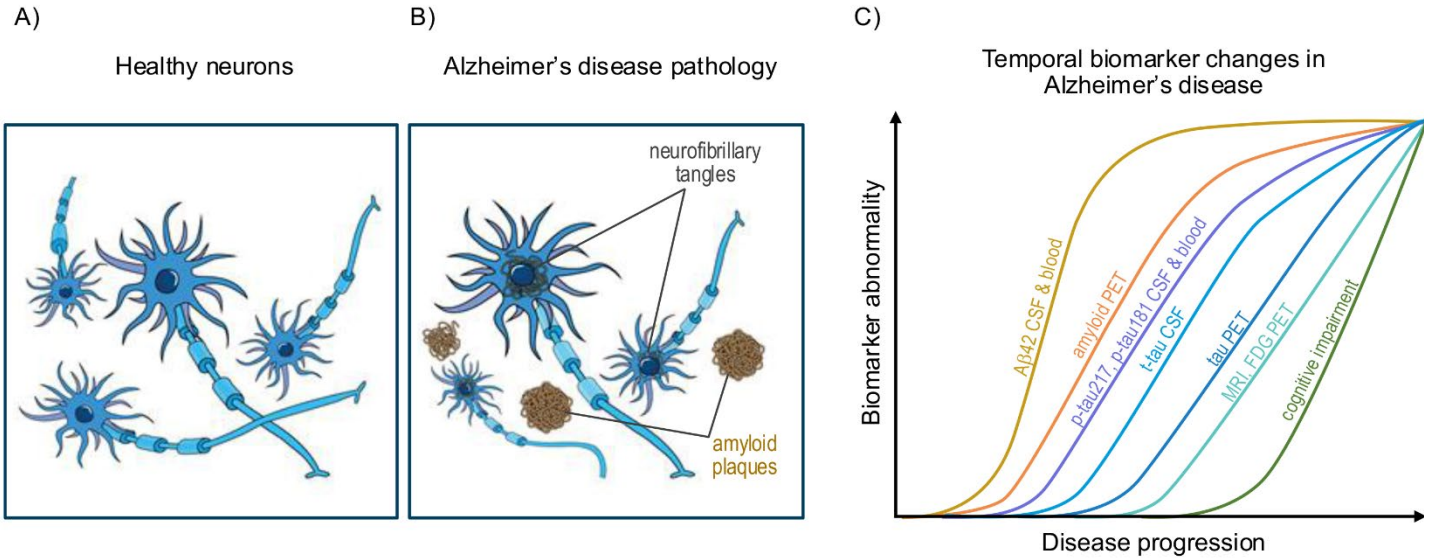

Figure 1. Alzheimer's disease neuropathology and core diagnostic biomarkers. (A and B) Alzheimer's disease neuropathology is characterized by the presence of amyloid plaques and tau tangles. (C) Neuropathological findings are reflected in biomarker changes over the course of disease. For biofluid biomarkers, lower concentrations of amyloid-β 1-42 (Aβ42) and higher concentrations of tau proteoforms are associated with Alzheimer's disease. The illustrated curves are intended to help conceptualize the sequential timing of biomarker changes.

2) CSF biomarkers

a) What are the core CSF biomarkers of AD pathology?

The primary characteristics of AD pathology are the progressive accumulation of amyloid plaques which are extracellular deposits of aggregated Aβ42, and other amyloid peptides surrounded by dystrophic neurites, reactive astrocytes and microglia, and intracellular deposits of hyperphosphorylated tau protein in neurofibrillary tangles (2, 31, 32). The core CSF biomarkers that detect AD pathology are Aβ42 alone, or the Aβ42/Aβ40 ratio, t-tau and tau phosphorylated in the threonine-181 position (p-tau181). The AD pathologic changes are reflected in CSF by decreased concentrations of soluble Aβ42 and the ratio Aβ42/Aβ40 and increased concentrations of t-tau and p-tau and the ratios t-tau/Aβ42 and p-tau181/Aβ42.

Other proteoforms of p-tau such as p-tau231, p-tau217, p-tau205 and microtubular binding region-tau (MTBR-tau) proteoforms are of interest for detection of early stages of tau pathology and amyloid plaque burden (p-tau231, p-tau217) or of later stages of tau pathology (p-tau205, MTBR-tau243) (15, 33). Although of research interest, these biomarkers in CSF have not yet undergone the required rigorous validation for use in clinical practice and will not be considered further in this guidance document.

Concentrations of other biomarkers of neurological injury or damage such as neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) may be elevated to varying extents over the time course of AD. However, these biomarkers are not specific to AD and are considered nonspecific biomarkers of

neurodegeneration (NfL) and astroglial activation (GFAP) (34, 35). Although of interest in research, they have inadequate diagnostic performance to be used in the differential diagnosis of cognitive decline suspected to be due to AD.

Key points:

- Aβ42 (with or without Aβ40), p-tau181 and t-tau are the core AD biomarkers in CSF.
- At present, other CSF tau proteoforms have not been sufficiently studied to serve as core AD biomarkers.

b) Which CSF biomarkers have the highest diagnostic accuracy/clinical validity for the detection of AD pathology?

Each of the three biomarker ratios—Aβ42/Aβ40, tau/Aβ42 and p-tau181/Aβ42—have independently demonstrated the highest diagnostic utility for detection of AD pathology, outperforming the individual biomarker components (7, 36-38). For example, p-tau181/Aβ42 has a percent agreement range with amyloid PET of 87-93% (overall), 89-97% (positive agreement) and 83-94% (negative agreement) across various cohorts (37). In the same study, the use of Aβ42 alone showed a percent agreement range with amyloid PET of 68-76% (overall), 91-92% (positive agreement) and 58-70% (negative agreement) (37).

Key point:

In CSF, ratios of p-tau181/Aβ42, tau/Aβ42 and Aβ42/Aβ40 have the highest diagnostic accuracy for identification of Alzheimer's pathology.

c) What are appropriate clinical indications for AD CSF biomarker testing?

Appropriate indications for testing include ruling in/out AD pathology in a symptomatic individual in the context of both pharmacological and non-pharmacological therapeutic considerations. From the pharmacological perspective, a current requirement for prescribing an anti-amyloid-β immunotherapy is objective biomarker findings of AD pathology (29, 30). From the non-pharmacological perspective, there are many potential uses and advantages of an early and accurate diagnosis including lifestyle interventions (39), increased counseling and connection to community resources (27, 28), as well as, enabling patient/family long-term planning and decision making (28). The Alzheimer's Association convened a multidisciplinary workgroup that developed guidance for the safe and optimal use of lumbar puncture and CSF testing for AD pathology, which includes clinical indications for appropriate use of AD core CSF biomarkers (**Figure 2**) (40). A detailed clinical and cognitive evaluation prior to CSF AD testing is of fundamental importance in each of the below appropriate indications, as is pre- and post-test counseling for the patient or substitute decision maker.

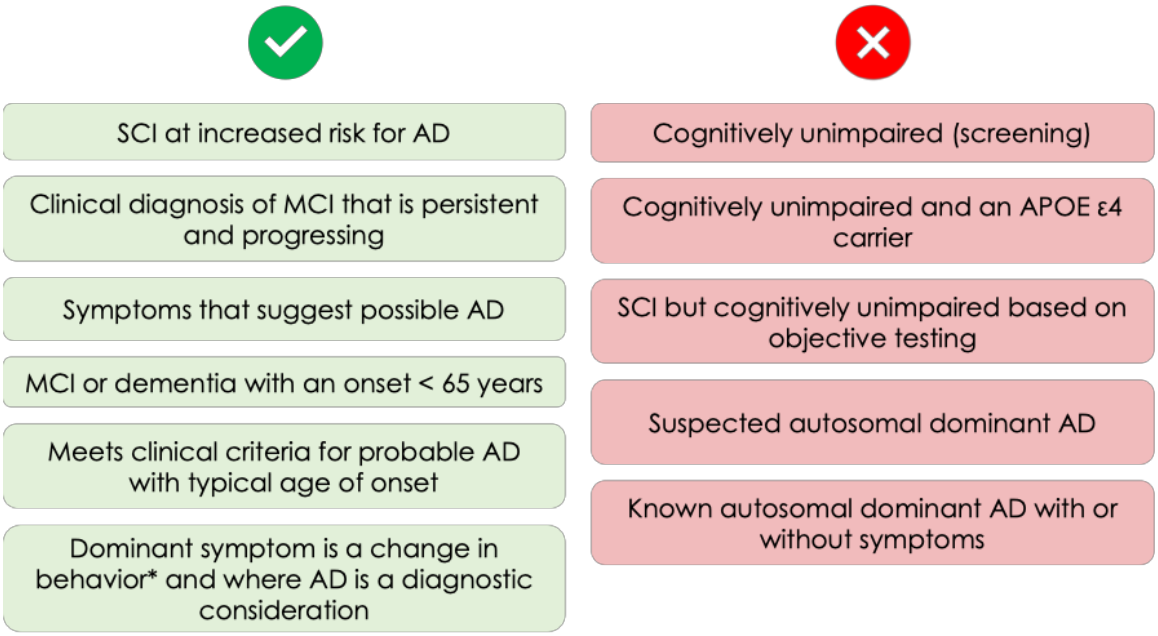

Figure 2. Appropriate (✔) and inappropriate (×) clinical indications for use of Alzheimer's disease core CSF biomarkers

(SCI: subjective cognitive impairment; MCI: mild cognitive impairment; AD: Alzheimer's disease; *examples of changes in behavior include Capgras syndrome, paranoid delusions, unexplained delirium, combative symptoms, and depression).

Key point:

CSF biomarker testing should only be used in symptomatic individuals where AD is a diagnostic consideration.

d) What are key preanalytical considerations in the assessment of AD CSF biomarkers?

The special pre-analytical handling requirements for CSF AD biomarker testing (**Table 1**) are a result of the relatively high hydrophobicity and aggregation propensity of Aβ peptides (41). If appropriate and validated pre-analytical procedures are not followed, there is a risk of losing Aβ peptides to surface adsorption and precipitation from solution due to self-aggregation. Loss of Aβ peptides in the pre-analytical phase represents a substantial patient risk as a low Aβ42 concentration may be interpreted as an AD biochemical signature (i.e., a false positive result). Tau proteoforms in CSF, on the other hand, are more robust to variations in pre-analytical conditions. Conditions suitable for Aβ peptides are thus generally suitable for measurement of tau proteoforms.

Aβ peptide adsorption can occur with any surface that comes into contact with the specimen including not only the collection tube, but also plastics used during the LP procedure such as extension tubing and syringes, as well as plastics used in specimen processing (e.g., pipet tips and additional aliquot tubes) (41) and in the analytical phase (42). Adsorption is exacerbated by certain materials (e.g., glass and polystyrene (43) and a

high surface to specimen volume ratio (44). As such, CSF is recommended to be collected via gravity drip, directly into a low binding polypropylene tube without the use of extension tubing or syringes (41). For greatest accuracy, it is ideal if no specimen transfer occurs from the point of collection to the point of analysis as even a single tube transfer can result in analyte loss (45). Assays with regulatory approval, i.e., in vitro diagnostic assays, provide specific pre-analytical protocols for CSF collection as part of their instructions for use. To achieve the best clinical performance, these recommendations should be followed, given that handling differences may impact the Aβ42 measured concentration, and its interpretation (both alone and as a ratio with the other core biomarkers).

Table 1. Preanalytical considerations for CSF Alzheimer's disease biomarker testing.

Phase	Pre-analytical consideration	Reason
Lumbar puncture	Morning collection	Diurnal variation
	Collection of 2nd or later fraction	Avoidance of cellular debris and blood contamination
	Collection by gravity drip direct into a polypropylene tube with a low propensity to bind proteins	Minimize loss of Aβ peptides to adsorption to surfaces
	Polypropylene collection tube optimized for CSF volume to tube surface area (e.g., required fill-line noted)	Minimize loss of Aβ peptides
Sample processing	Minimal to no intervention (e.g., no aliquoting, only centrifuge if debris present)	Minimize loss of Aβ peptides
Shipment	Ship via temperature- and protocol-validated method	Avoidance of freeze/thaw cycles
Storage prior to analysis	If properly collected, sample can be stored frozen for prolonged periods	Enables shipment to analysis site & "add-on" testing

Key points:

- Clinical laboratories should establish and follow special collection, processing, analysis, and storage protocols for AD core biomarker testing.
- Protocols established for Aβ peptides (due to their propensity for aggregation and surface adsorption) are generally suitable for tau proteoforms.
- Due to the risk of a false positive AD interpretation, improperly collected specimens yielding a positive result may require test cancellation and specimen recollection.

e) What are current reference methodologies and routine clinical methodologies used for the measurement of the core AD CSF biomarkers?

Prior to the development of fully automated immunoassays for CSF Aβ42, Aβ40, total-tau and p-tau181, the earlier research use only (RUO) manual immunoassays suffered from high variability and lacked standardization (46, 47). Recognition of the need for standardization using antibody-independent reference methodology and CSF-based certified reference materials (CRMs) led the Alzheimer's Association Global Biomarker Standardization Consortium (GBSC) to support the development of mass spectrometry reference methodology and CRMs (48). In connection with this GBSC effort, an International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) workgroup "Biomarkers of Neurodegenerative Diseases" was charged with development of reference methodology and CRMs for Aβ42, Aβ40 and t-tau in CSF and p-tau217 in plasma.

Aβ42: Two reference methods for Aβ42 in CSF using liquid chromatography tandem mass spectrometry (LC-MS/MS), C12RMP1 (49) and C11RMP9 (50), have been approved by the Joint Committee for Traceability in Laboratory Medicine (JCTLM). CSF Aβ42 CRMs are available with value assignments based upon assays from five different reference laboratories each using LC-MS/MS and a common Aβ42 calibration standard (51). It is recommended that clinical laboratories use assays with calibration traceable to these CRMs. Fortunately, most regulatory approved Aβ42 assays available in the US and Canada meet this criterion.

Aβ40: There is one JCTLM-recognized LC-MS/MS reference method for Aβ40 (C16RMP2R) (52) and others are in development. The planning phase for a CSF-based CRMs is underway.

Tau proteoforms: Currently there are no reference methods, nor CRMs, for tau proteoforms. A t-tau CRM is in development (53).

Key points

- For CSF Aβ42, clinical laboratories should use assays with calibration traceable to established CRMs.
- For CSF Aβ40, a reference method is available with CRMs anticipated in the near term.
- For CSF t-tau and p-tau, reference methods and CRMs are still in development
- As a result, assays for CSF Aβ40, t-tau and p-tau are currently neither standardized nor harmonized.

f) What are the key considerations in the reporting and interpretation of AD CSF biomarkers?

Reporting of CSF biomarkers should include numeric values (concentrations and ratios), medical decision limit(s), and an overall interpretative comment. Best laboratory practice is to report both the individual biomarker concentrations and the relevant ratio(s), e.g., Aβ42/Aβ40, p-tau181/Aβ42, and/or t-tau/Aβ42. The ratios are a necessity given their higher diagnostic performance, and the individual biomarker concentrations enable a more accurate interpretation of the biomarker profile in various clinical contexts (discussed further

below). While this represents best practice, laboratories may be limited by their accreditation and/or regulatory requirements given that some IVD products obtained regulatory approval only in consideration of biomarker ratios.

Current assays with regulatory approval in Canada and the US have been optimized for older individuals (predominantly from cohorts with individuals 55 years and older) presenting with symptoms of cognitive impairment and being evaluated for AD. The interpretation of the ratios is based on medical decision limits (not reference intervals) that have been optimized based on their concordance with amyloid PET status as an indicator of AD pathology. As such, a negative CSF result based on the biomarker ratio is consistent with a negative amyloid PET result; a positive result based on the biomarker ratio is consistent with a positive amyloid PET result. In clinical practice, the diagnosis of AD is not made solely on the basis of a biomarker ratio result; rather physicians integrate this information with various factors into their assessment when establishing a diagnosis.

For biomarker reporting by the laboratory, the interpretive diagnostic comment should include a statement to the consistency of the biomarker profile with the presence or absence of AD pathology. Other information that would be helpful to make readily available to physicians includes the performance of the test such as the positive and negative predictive value in the intended use population, the intended use population (symptomatic individuals) from which the performance characteristics were derived, and consideration of other factors that might affect test accuracy.

The latter includes a reminder of the importance of preanalytical considerations, and the potential for co-pathologies/alternate pathologies. The presence of other pathologies alone, or in combination with AD, may affect the core AD CSF biomarkers and thus their interpretation. For example, Creutzfeldt-Jakob disease (CJD) and CSF dynamic disorders such as normal pressure hydrocephalus (NPH) can result in misinterpretation of the core AD biomarkers. In CJD, rapid neuronal loss can cause a substantial increase in t-tau, possibly resulting in an abnormal t-tau/Aβ42 ratio (54). If one were interpreting the biomarker panel solely based on this ratio, these findings would be considered “consistent with AD pathology” despite not being driven by an AD pathological process. In another example, with NPH, low concentrations of all the core biomarkers (Aβ42, Aβ40, p-tau an t-tau) are commonly observed. These biomarker abnormalities may reflect CSF flow disturbances and/or comorbid AD neuropathology (55). Thus, understanding and accounting for the complexity of CSF AD biomarkers is crucial for accurate interpretation.

For an overview of general interpretive comments and considerations, readers are directed to a synthesis of clinical reporting of AD CSF biomarker results which included 40 centers located in 15 different countries (56).

Key points

- Ratios of the AD CSF biomarkers must be included in the report as they have the highest diagnostic accuracy for the identification of Alzheimer's pathology.
- Other pathologies and co-pathologies can affect AD core CSF biomarker concentrations and ratios; clinical laboratories should communicate these interpretive limitations to the health care provider.

3) Blood biomarkers

a) What are the core blood biomarkers of AD pathology?

Early efforts at AD blood biomarker development mirrored those for CSF, initially focusing on Aβ42 and Aβ40. With Aβ concentrations 10-20-fold lower in plasma as compared to CSF, the ability to reliably measure these analytes in plasma required significant improvements in analytical sensitivity and focused on two technologies immunoprecipitation-mass spectrometry (IP-MS) and two-site sandwich immunoassays (57-59). The diagnostic challenge is significant: while CSF Aβ42/Aβ40 ratios drop ~50% in AD compared to controls, plasma Aβ42/Aβ40 ratios decrease only ~10%–15% (60). This smaller difference makes plasma assays vulnerable to diagnostic misclassification from small drifts in assay performance and/or pre-analytical variations, which currently limits the clinical utility of plasma Aβ42/Aβ40 (61).

While plasma tau biomarker assays faced similar analytical hurdles (concentrations are 10-20-fold lower than CSF), plasma tau biomarkers are less vulnerable to pre-analytical variations. Currently, p-tau217 is the most robust tau-related plasma biomarker (19, 62, 63), demonstrating superior sensitivity and specificity for detection of AD pathology compared to other tau phosphorylation sites (64, 65). Notably, plasma p-tau217 concentrations correlate more strongly with amyloid pathology than with tau tangle pathology, suggesting it is released from neurons as part of the complex response to amyloid pathology (66).

In addition to Aβ and tau proteoforms, several other biomarkers related to AD pathobiology can be measured in plasma or serum. These include NfL and GFAP, and like in CSF, these biomarkers have inadequate diagnostic performance to be used in the differential diagnosis of cognitive decline suspected to be due to AD (67).

b) Which blood biomarkers have the highest diagnostic accuracy/clinical validity for the detection of Alzheimer's pathology?

The diagnostic accuracy and clinical validity of AD blood biomarkers depend on both the biomarker and the specific assay used for measurement. Assays for p-tau217 include those measuring only the phosphorylated form (p-tau217), the ratio of phosphorylated to non-phosphorylated p-tau217 (%p-tau217) and the ratio of p-tau217 to Aβ42 (p-tau217/Aβ42) . Select p-tau217 assays have demonstrated performance equivalent to CSF AD biomarkers for detecting AD pathology, achieving receiver operating characteristic area under the curves of ≥0.90 (62, 65). Therefore, the 2024 Revised Criteria for Diagnosis and Staging of AD has endorsed p-tau217 assays with ≥90% accuracy as an acceptable diagnostic biomarker, in symptomatic individuals (68).

Blood biomarker assays for p-tau181 (62, 63), p-tau231 (62), and Aβ42/40 ratio (69) have also been evaluated for the identification of AD pathology. These assays either do not meet the minimal performance recommendations for confirmatory testing or fall short of the performance of p-tau217 (18, 70). This applies to both laboratory-developed tests (LDT) and regulatory cleared tests.

At the time of preparation of this document, there are regulatory approved plasma p-tau217 and p-tau181 options in the US and many others in the regulatory pipeline in both the US and Canada. Readers should refer to the US Food and Drug Administration and Health Canada medical device databases for the most up to date information (71, 72). In addition, LDT options are available in the US and Canada.

Key points

For blood testing, clinical laboratories should prioritize selection of p-tau217 assays (alone or as a ratio) over p-tau181, p-tau231, and Aβ42/40, as p-tau217 demonstrates the highest diagnostic accuracy for Alzheimer's pathology.

c) What are currently recommended clinical indications for AD blood biomarker testing?

i) Intended use applications

Currently available blood AD biomarker tests are categorized as either triage tests or confirmatory tests based on their diagnostic performance (70). Triage tests have high negative predictive value for ruling out AD pathology; a negative result is consistent with the absence of AD pathology, while a positive result necessitates further diagnostic workup due to their low specificity (Table 2).

Confirmatory tests are intended to identify AD pathology without additional testing, similar to CSF biomarkers or amyloid PET. Confirmatory tests are appropriate for secondary or tertiary care settings where the patient population has a higher pre-test probability for AD. Confirmatory blood biomarker results must be interpreted in conjunction with comprehensive clinical and cognitive assessment and may not eliminate the need for confirmation by amyloid PET or CSF biomarkers.

Table 2. Performance recommendations for blood biomarkers of Alzheimer's pathology.

Type of test	Minimum acceptable sensitivity	Minimum acceptable specificity
Triage	90%	75-85%*
Confirmatory	90%	90%

***** When access to follow-up testing is limited, minimum acceptable specificity is 85%. Performance specification assumes patient is symptomatic (i.e., moderate to high prevalence setting.) (70)

A multidisciplinary group convened by the Alzheimer's Association has developed a clinical practice guideline for the use of blood biomarkers in the diagnostic evaluation of individuals with mild cognitive impairment or

dementia who are being assessed in specialized care settings and where AD is the suspected underlying etiology (73). The recommendations are informed by a review of the literature on various blood biomarkers assays using a single cut-point for result interpretation. The key recommendations are (1) blood biomarker tests with at least 90% sensitivity and 75% specificity may be utilized as triage tools, and (2) blood biomarker tests with ≥90% sensitivity and specificity may be used as an alternative to amyloid PET or CSF AD biomarker assessments. Importantly, the guideline emphasizes considerable variability in diagnostic accuracy across available tests, noting that many commercially available blood biomarker tests do not meet these performance specifications, particularly when a single cutoff value is used. While not addressed in the guideline (73), it is now common to employ two cutpoints (rule-in and rule-out, along with an intermediate zone), in order to achieve the desired diagnostic accuracy characteristics (discussed in greater detail in Section 3.f). Such performance considerations are important for laboratories when selecting blood biomarker tests for implementation or referral purposes.

ii) Intended use populations

Current recommendations limit the use of AD blood biomarkers to individuals meeting all criteria below:

- Cognitive decline, mild cognitive impairment or dementia, and,
- AD in the differential diagnosis, and,
- Evaluation occurring in specialized care settings (e.g., memory clinic).

AD blood biomarkers are not intended to replace clinical evaluation and should only be utilized following a thorough clinical assessment (74).

At the time of this publication, AD blood biomarkers are not recommended for [71, 4]:

- Primary care settings;
- Cognitively unimpaired individuals (including those with family history);
- General population screening;
- Direct-to-consumer testing.

AD blood biomarker testing in the primary care setting could theoretically improve timely diagnosis and care equity for individuals with limited specialty care access (74). However, significant limitations exist including: insufficient studies on assay performance in primary care populations, unclear effects of comorbidities on test interpretation, absent consensus guidelines for primary care use, and inadequate education resources for clinicians and patients regarding result interpretation (75, 76). AD blood biomarker testing in the primary care setting *may* be appropriate if:

- The individual has objective cognitive decline as determined by a full clinical workup, with treatable sources of cognitive decline ruled out (74).
- The symptomatic individual is at least 55 years old (if using a triaging test) or at least 65 years old (if using a confirmatory test) (70, 74)

- The primary care provider understands the performance of the test being ordered and is comfortable interpreting the test results and discussing the results with the patient (74).

The inclusion of age restrictions in the primary care setting, as well as the need for determination of cognitive decline, are intended to increase the pre-test probability given the lower prevalence of AD in this population.

iii) Anti-amyloid therapies

Eligibility for anti-amyloid therapies for the treatment of AD requires confirmation of AD pathology, which is currently accomplished via amyloid PET or CSF AD biomarker testing. The addition of accurate AD blood biomarkers (i.e. those with >90% accuracy) to the diagnostic criteria (5) has the potential to increase equitable access to these therapies. Although AD blood biomarkers may be incorporated into the diagnostic assessment for determining eligibility for anti-amyloid therapies, clinicians continue to depend on CSF biomarkers or amyloid PET for confirmation of AD pathology. There are no biofluid biomarkers currently recommended for use in monitoring response to anti-amyloid therapy, optimizing dosage, determining cessation/re-starting of therapy, or monitoring for side effects.

Key points

- For blood biomarkers of Alzheimer's pathology, clinical laboratories should:
  - Classify assays as triage or confirmatory based on their diagnostic performance.
  - Promote appropriate test utilization, which, based on current guidelines, is limited to individuals with objective cognitive decline suspected to be due to AD presenting in specialty care settings.
- In the context of anti-amyloid therapies, clinical laboratories should recognize that blood testing is:
  - Recommended as part of the diagnostic workup for AD, though confirmatory testing using CSF biomarkers or amyloid PET may still be required.
  - Not recommended for monitoring treatment response or for informing dose adjustment.

d) What are key preanalytical considerations for the assessment of AD blood biomarkers?

Various preanalytical handling studies have been reported in the literature for plasma Aβ42/40, p-tau181 and p-tau217 (77-81). A comprehensive study evaluating the impact of tube type, hemolysis, centrifugation delays/settings, storage conditions, and freeze-thaw cycles on Aβ peptides (Aβ42, Aβ40) and p-tau proteoforms demonstrated that Aβ peptides are most susceptible to variations in preanalytical handling, whereas p-tau proteoforms are highly resistant to variations in pre-analytical sample handling (81). Additional studies are needed to understand preanalytical variables not associated with sample handling, such as the effect of fasting, comorbidities, circadian rhythm, and medication usage.

Common guidance for laboratories includes freezing samples not analyzed within 24 hours of collection, and the use of K2 or K3 EDTA plasma collection tubes as a universal tube for both p-tau217 and Aβ peptides, as

the EDTA acts as an inhibitor of plasma proteases which can contribute to *in vitro* degradation of Aβ peptides (82).

For in vitro diagnostic assays, preanalytical guidance will be provided by the manufacturer and should be verified by the laboratory, otherwise the laboratory must establish pre-analytical conditions for each individual biomarker/assay prior to clinical use. Published sample handling workflows can offer helpful suggestions when laboratories need to develop their own pre-analytical procedures (81).

Key points

- Clinical laboratories should evaluate the impact of preanalytical factors on AD blood biomarker assays prior to clinical implementation.
- Aβ peptides in blood, as in CSF, have more stringent preanalytical requirements than tau proteoforms.

e) What are current reference methodologies and routine clinical methodologies used for the measurement of AD blood biomarkers?

There are currently no certified reference materials nor reference methods for AD blood biomarkers. As such, assay manufacturers currently must develop or procure their own purified materials for calibration, which has resulted in highly variable calibration schemes between manufacturers. Regulatory approved AD blood biomarkers assays are not standardized, resulting in variations in measured analyte concentrations across different assay platforms.

For routine measurement in the clinical laboratory, both Aβ and tau proteoforms are measured in blood predominantly by one of two techniques: immunoassay and/or mass spectrometry. There are additional methodologies used in research settings, but these are outside of the scope of this document. In vitro diagnostic manufacturers have developed relevant plasma assays on their routine high-volume immunoassay analyzers. As such, there are fully automated options for analysis of AD blood biomarkers including Aβ42, Aβ40, p-tau181 and p-tau217. Assays in this class are non-competitive two-site sandwich immunoassays. They use monoclonal capture and detection antibodies for analyte specificity reasons, and detection via luminescence in order to achieve the analytical sensitivity required for these relatively low abundance biomarkers.

Targeted mass spectrometry methods also exist, which involve complex sample preparation including immuno-enrichment (to improve analytical sensitivity), followed by proteolytic digestion and quantification of the target analyte's proteolytic peptides. With automated immunoassay analyzers using instrumentation already common to clinical laboratories, and with assay kits at various stages of regulatory approval, immunoassays are a more accessible and practical option for testing for the majority of clinical laboratories.

Understanding analytical differences between methodologies and manufacturers is important for laboratories when selecting assays for local implementation or referral. Differences in analytical sensitivity and precision may influence test performance. Analytical sensitivity determines the proportion of results falling below the assay's limit of quantitation and may vary significantly between assays; inferior analytical sensitivity may reduce effectiveness for detecting amyloid pathology. Assays with high impression may increase diagnostic uncertainty for values at or near the medical decision limits, thereby affecting their clinical discrimination.

Key points

- For blood AD biomarker testing, immunoassays are the most accessible and practical option for clinical laboratories, with options available on fully automated clinical analyzers.
- These assays are currently neither standardized nor harmonized due to the absence of CRMs and reference methods; results across manufacturers should therefore not be directly compared.

f) What are the key considerations in the reporting and interpretation of AD blood biomarkers?

Interpretation of AD blood biomarkers is based on assay specific medical decision limits and the biomarker context of use. Guidelines for the minimum acceptable clinical performance of AD blood biomarker tests for triaging or confirmation of AD pathology have been described and should be followed when evaluating test performance (70). In contrast to CSF biomarkers, which show clear differentiation between amyloid PET-positive and amyloid PET-negative groups, 5-20% of AD blood biomarker results exhibit overlap between these two categories (83, 84). Employing a single cutpoint for classification can result in an undesirable rate of false positive or false negative results. Consequently, a two-cutpoint approach is commonly employed for reporting AD blood biomarker results—positive, intermediate, and negative—to improve the diagnostic accuracy for both positive and negative results (84). When utilizing this model, no more than 20% of individuals should be classified as having intermediate results (84). Individuals with an intermediate result would require follow-up confirmatory testing such as CSF AD biomarkers or amyloid PET.

Reporting of AD blood biomarkers should include enough information to help clinicians interpret the numeric value provided in the report. The laboratory report and/or laboratory test catalogue should include information on the: intended use (triaging or confirmatory test), intended use population, test clinical performance (e.g., positive and negative predictive value in the intended use population), and factors that might affect the accuracy of the test result (e.g., comorbidities and medications). If a two-cutpoint approach is used for reporting, guidance on how to interpret results in the intermediate range and the recommended testing follow-up for these individuals.

Confounding factors, such as comorbidities and medications, which might influence blood biomarker concentrations, have not been as extensively studied. Comorbidities such as diabetes mellitus, chronic kidney

disease (CKD), increased body mass index, history of stroke, and myocardial infarction (MI) have been reported to alter certain blood biomarker concentrations (85). Efforts to better understand the impact of impaired renal function are ongoing (86, 87). Modestly higher plasma p-tau217 concentrations were found to be associated with more advanced stages of kidney dysfunction (87); however, further research is required to determine whether these modestly higher concentrations will confound the diagnosis of AD when established medical decision limits are applied. Certain medications have been found to affect the plasma concentrations of select biomarkers (88, 89). For example, the cardiac drug sacubitril/valsartan has been reported to reduce the plasma Aβ42/40 ratio by ~33%, potentially causing a false positive interpretation of plasma Aβ42/40 results (89). Limited and conflicting data is available regarding the influence of food intake on the concentration of blood biomarker (90). Large studies covering the full spectrum of comorbidities are needed to better define whether any of these confounders significantly affect the clinical interpretation beyond the expected analytical and biological variability.

Key points

- Reporting and interpretation of blood AD biomarkers may require the use of a two-cutpoint approach to achieve the desired test accuracy.
- The test report and/or the laboratory test catalog should include information to facilitate interpretation by the ordering physician including:
    - Clinical performance (e.g., positive and negative predictive values) and population characteristics from which these metrics were derived (e.g., disease prevalence, race/ethnicity, age, etc.).
    - Comorbidities and medications that may affect the accuracy and/or interpretation of the test result.

4) Analytical validation and quality assurance

a) What are the key considerations in the validation of AD CSF and blood biomarker assays?

Analytical validation of AD CSF and blood biomarker tests should adhere to the requirements set by the laboratory's regulatory bodies, including assessments of sample stability, precision, accuracy, reportable range, and other relevant parameters. In general, AD CSF biomarkers are highly correlated across different assay manufacturers (91-93), but systematic bias exists and absolute concentrations may vary widely. The same holds true for p-tau217 assays. CSF Aβ42 is the only AD biomarker traceable to a CRM, therefore assays with calibration traceable to this CRM demonstrate less bias. Full commutability across vendors, however, has not been achieved (93). These limitations must be considered when conducting method comparison studies,

verifying medical decision limits, and any other studies employing data and/or analyses across more than one manufacturer's product.

Reference intervals are not used for these biomarkers. Instead, interpretation is based on agreements with established measures of AD neuropathological changes. For CSF biomarkers, this includes amyloid PET and/or post-mortem neuropathology neuropathological examination. For plasma biomarkers, the presence of AD pathology is commonly determined using AD CSF biomarkers. Given the observed bias across different assay manufacturers for both CSF and blood biomarkers, it is essential for the laboratory to provide assay-specific medical decision limits.

Clinical validation might be required depending on the regulatory classification of the test. If the laboratory offers an LDT, a clinical validation study should be performed to establish medical decision limits and define the test's clinical performance characteristics or clinical validity in the intended use population. Alternatively, published medical decision limits might be adopted if the laboratory uses the same assay kit and can demonstrate acceptable accuracy compared to the assay described in the published literature. When using an assay with regulatory approval, clinical validity will have been established by the manufacturer, and the laboratory should assess applicability of the validation cohort used by the manufacturer for the population in which the test will be used. While there are no guidelines for recommended clinical performance verification, it is best practice for the laboratory to verify the manufacturer's clinical performance claims. In these situations, having access to samples with supporting clinical and neuropathological data would be required.

For AD CSF biomarkers validation, the most significant challenges are the availability of samples collected/processed/stored following the required pre-analytical protocols, and for assessments of diagnostic performance, the supporting clinical and neuropathological data (or surrogates thereof) for these samples. Biomarker stability needs to be considered when using stored samples, in particular for Aβ42. Similar to CSF, the most significant challenge for clinical laboratory validation of AD blood biomarkers would be supporting clinical and neuropathological data (or surrogates thereof) on the samples used for the diagnostic accuracy study.

b) How can laboratories monitor AD CSF and blood biomarker assay performance?

Clinical laboratories seeking to participate in a proficiency testing/external quality assessment program may employ the University of Gothenburg's quality control program (formerly known as the Alzheimer's Association external quality control program) (94). The intent of this program is to assess variability in biomarkers measurements and compare results between laboratories; it is not an accuracy-based program. While participants receive a report summarizing their performance in comparison to other participant laboratories after each round, the results are not graded, and it is the laboratory's responsibility to evaluate the results for acceptability. Data on assays and laboratories performance included in the program has been previously published (46) and accessible on the program website with approximately 200 laboratories participating (95).

Other proficiency testing/external quality assessment programs are in development, but are not available for formal enrollment at the time of publication of this document.

Key points

- Clinical laboratory analytical validation/verification of AD biomarkers should adhere to the requirements of the applicable regulatory body.
- Implementation as an LDT would require the clinical laboratory to define and clinically validate medical decision limit(s).
- A critical aspect of the validation/verification process for AD CSF biomarkers includes access to relevant clinical specimens collected following acceptable pre-analytical parameters.
- At the time of preparation of this document, formal proficiency testing/external quality assessment options are limited; clinical laboratories may need to implement an alternative proficiency testing approach.

5) Other biomarkers of relevance in AD

a) *Genetic testing for autosomal dominant AD*

AD can be broadly divided into three types, sporadic AD (~75% of cases), familial AD (~15-20% of cases) and autosomal dominant AD (<5%) (96, 97). Autosomal dominant AD is defined as occurring in at least three individuals in two or more generations with two of the individuals being first-degree relatives of the third. Autosomal dominant AD presents almost exclusively as early onset AD, and thus the two terms are often used interchangeably. Familial AD is defined as occurring in more than one individual, where at least two of the affected individuals are third-degree relatives or closer.

There are three known causative genes where pathogenic variants cause autosomal dominant AD: *PSEN1, PSEN2, and APP.* Notably, pathogenic variants in *APP* and *PSEN1* have complete penetrance, whereas those in *PSEN2* have 95% penetrance (96, 97). Given that pathogenic variants in these three genes have not been detected in all cases of early onset AD, it is suspected that there are additional, yet discovered, genetic components.

Genetic counseling and testing in the context of suspected early onset AD is described in detail in the American College of Medical Genetics and Genomics practice resource (97).

b) *Apolipoprotein E (APOE) genotyping*

Single-nucleotide polymorphisms in *APOE* result in three major apoE proteoforms based on amino acid differences at residues 112 and 158: apoE-ε2, apoE-ε3, and apoE-ε4. ApoE-ε4 is one of the strongest known genetic risk factors for late onset AD; however, the ε4 allele is neither necessary nor sufficient to cause AD (97). As a result, *APOE* genotyping is not recommended for predicting AD.

APOE genotyping is recommended for the assessment of risk of amyloid-related imaging abnormalities (ARIA) in the context of the current formulation and delivery of two anti-amyloid therapies: lecanamab and donanemab. This recommendation stems from clinical trial data demonstrating a higher incidence of ARIA in ε4 homozygotes, followed by ε4 heterozygotes, as compared to non-carriers (29, 30). In addition, to *APOE* genotyping, apoE-ε4 proteotyping assays (quantitative plasma apoE-ε4 immunoassays) are in development on automated immunoassay analyzers for determination of apoE-ε4 carrier status and may serve as a future alternative to genotyping. Currently, there are no regulatory approved assays for APOE genotype or apoE-ε4 proteotyping available.

c) *Protein biomarkers beyond* Aβ *and tau proteoforms*

A few established genetic biomarkers, emerging protein biomarkers and those frequently used in research are noted in **Table 3**. A comprehensive review of such biomarkers is beyond the scope of this guidance document, and readers are directed to the literature for the most current information. In brief, beyond the core AD biomarkers discussed above, no other biomarkers are currently recommended for the diagnosis of AD. From a diagnostic perspective, non-specific markers of neuronal inflammation/injury or astrogliosis, such as NfL and GFAP, have insufficient and/or inconsistent discriminatory power (67, 98). These and other biomarkers, such as additional tau proteoforms, have demonstrated correlation with select aspects of pathobiology, which can be useful in research settings (5).

Table 3. Other biomarkers of relevance in AD.

Biomarker	Clinical application or role in pathobiology	Clinical utility rating in AD
APP, PSEN1, PSEN2	Suspected familial AD	High
***APOE* genotyping**	AD risk	Low
***APOE4* genotype or apoE-ε4 proteotype**	ARIA risk assessment and treatment eligibility in the context of anti-amyloid therapies	High
Neurofilament light chain (NfL)	• Marker of axonal damage • Non-specific marker of neurodegeneration • May be elevated in neurodegenerative disorders, non-neurodegenerative neurological pathologies, behavioral disorders (e.g., alcohol use disorders), etc.	Low – used in research
Glial fibrillary acidic protein (GFAP)	• Marker of astrocyte activation	Low – used in research
Other tau proteoforms: other phosphorylations [e.g., 205, 231], microtubule-binding region forms, etc)	• Of the tau proteoforms, p-tau217 has the highest diagnostic accuracy for AD pathology • Specific tau proteoforms may correlate differentially with distinct aspects of pathobiology	Emerging – under investigation

Key points

- Genetic counseling and testing for pathogenic variants may be appropriate in the context of suspected early onset AD.
- *APOE* genotyping is recommended for assessment of ARIA risk prior to initiation of anti-amyloid therapy.
- *APOE* genotyping is not recommended for assessing risk for developing AD.
- NfL and GFAP are not recommended for the diagnosis of AD.

6) Conclusion

Biofluid biomarkers have fundamentally transformed the diagnostic landscape for AD, enabling objective detection of underlying pathology before severe cognitive decline occurs. CSF biomarkers (Aβ42/Aβ40, p-tau181/Aβ42, and t-tau/Aβ42 ratios) provide excellent diagnostic accuracy and remain the gold standard for biofluid testing. The emergence of blood biomarkers, particularly p-tau217 assays achieving ≥90% diagnostic accuracy, represents a paradigm shift toward more accessible testing options.

Current appropriate clinical applications of both CSF and blood biomarker testing focus on diagnosis of symptomatic individuals in specialized care settings, with additional utility in evaluating anti-amyloid therapy eligibility. The recent availability of regulatory approved plasma assays marks a major shift in dementia care for both clinical teams and clinical laboratories. Implementation of biofluid AD assays, both CSF and blood, require careful consideration of preanalytical factors along with analytical and clinical performance in the intended use population, and interpretive support for clinicians.

Future developments hold tremendous promises for improving patient care. Ongoing standardization efforts through CRMs and reference methodologies will enhance measurement consistency across laboratories and assays. Expanded research into pre-clinical AD and primary care applications, combined with improved clinician education and decision support tools, are also underway. As is the development of biomarkers for AD co-pathologies which aim to provide more comprehensive diagnostic insights.

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Authors' Disclosures or Potential Conflicts of Interest

Upon manuscript submission, all authors completed the author disclosure form.

Research Funding

None.

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