Alzheimer's Association's Evidence-based Clinical Practice Guideline on the Use of Blood-based Biomarkers in the Diagnostic Workup of Alzheimer's Disease within Specialty Care: Request for Public Comments on Recommendations and Remarks

What is the ask:

- **Panel recommendations and remarks (Table 1):** Please review the information starting on Page 2. Use the **online form** to provide feedback on the content or presentation of what are to be **regularly updated** recommendations and associated remarks contained in the green column in **Table 1**. **Overall, we wish to understand if you believe the recommendations are 1) Clear and 2) Actionable and 3) If not, please provide suggestions for how to improve their usefulness for clinical decision-making.** Your diverse perspectives are essential to ensuring the recommendations are practical, patient-centered, and reflective of real-world experiences. We have also provided a legend (Table 2) informing the interpretation and implementation of these draft recommendations by various users.

- Our guideline development process and methodology (Pages 5-10): **For context only**, we briefly describe the overview of the guideline development process, including systematic review methodology. In addition to finalized recommendations and remarks, a full reporting of panel disclosures, summary of findings tables, and methods will be submitted to a scientific journal and peer-reviewed by external reviewers before approval for publication.

Who should comment:

- Clinicians across all disciplines and specialities, researchers**,** patients, caregivers, and family members of those affected by dementia, patient advocates, health system representatives, healthcare administrators, policy-makers, and any individual or organization with an interest or expertise in this topic can comment.

- If multiple individuals within the same organization/agency wish to provide feedback, we strongly encourage submitting a *single, comprehensive, coordinated response* that integrates all perspectives. This helps ensure clarity and coherence for panel review.

How your comments will be used:

- The methods team and guideline panel will review all feedback received during the public comment period **(May 12 - May 19, 5 p.m. CDT)**. Comments that are within the scope of the guideline question *and supported* by the available evidence will be considered for incorporation into the final guidance. Revisions may be made to improve accuracy, clarity, or applicability.

- Following the publication of the final manuscript, all comments—de-identified where possible—will be made publicly available to promote transparency and acknowledge the contributions of stakeholders..

Please scroll down to review recommendations and remarks in Table 1.

Table 1. Recommendations and remarks for clinical decision-making by clinical specialists

Clinical questions (closed for comment)	Recommendations and remarks (to be regularly updated)
Clinical question 1 (closed for comment): Should a blood-based biomarker (BBM) test* be incorporated as a **triaging** test† in the diagnostic work-up of individuals with cognitive impairment (including those with MCI or dementia) seeking specialized care for cognitive disorders?	**Recommendation statement 1 (open for comment):** In patients with objective cognitive impairment presenting to specialized memory-care settings, the panel suggests **for** the use of a BBM test as a triaging test in the diagnostic workup of Alzheimer's disease. (**Conditional recommendation, Low certainty evidence**). Tests with acceptable diagnostic test accuracy‡, based on current evidence, include: ● %p-tau 217 IP-MS, Washington University (WashU)§ ● %p-tau 217 IP-MS Precivity™, C2N Diagnostics ● p-tau 217 IP-MS Precivity™, C2N Diagnostics ● p-tau 217 Immunoassay, Lumipulse, Fujirebio ● Aβ42/40 HISCL Immunoassay, Sysmex **Remarks:** ● BBMs do not substitute for an appropriate clinical evaluation by a healthcare professional, and the test results should always be interpreted within the clinical context. In the following clinical scenarios, a BBM test may not be appropriate **(final manuscript will contain references and rationale for the following statements):** ● Patients who are not a candidate for, or who have already made an informed decision against anti-amyloid therapy after considering the risks and benefits, **AND** who do not wish to know their brain amyloid status. ● Patients with obvious modifiable or temporary contributors that could account for their cognitive impairment (e.g., depression, medication, untreated sleep disorder, acute grief, thyroid disorder). Clinicians may wish to treat these modifiable contributors first and confirm that objective cognitive impairment persists before deciding whether to order a BBM test. ● Patients with limited life expectancy due to very advanced age, as the clinical significance and prognosis of brain amyloid are not well-defined in these populations. ● Patients with a history of conditions that may impact amyloid or phosphorylated tau in plasma in ways that have not been well-studied (e.g., neurocysticercosis, history of chemotherapy or radiation, chronic traumatic encephalopathy). ● Patients with other medical comorbidities or medications that interfere with levels of a given BBM (e.g., severe chronic kidney disease, ALS).

Clinical question 2 (closed for comment): Should a blood-based biomarker (BBM) test* serve as a substitute for CSF analysis or amyloid PET as a **confirmatory** test in the diagnostic work-up of patients with cognitive impairment (MCI or dementia) undergoing specialty care evaluation for cognitive disorders?	**Recommendation statement 2 (open for comment):** In patients with objective cognitive impairment presenting to specialized memory-care settings, the panel suggests **for** the use of a BBM test as a confirmatory tool in the diagnostic workup of Alzheimer's disease. (**Conditional recommendation, Low certainty evidence**). Tests with acceptable diagnostic test accuracy#, based on current evidence, include: ● %p-tau 217 IP-MS,WashU§ **Remarks:** ● BBMs do not substitute for an appropriate clinical evaluation by a healthcare professional, and the test results should always be interpreted within the clinical context In the following clinical scenarios, a BBM test may not be appropriate **(final manuscript will contain references and rationale for the following statements)**: ● Patients who are not candidates for, or who have already made an informed decision against anti-amyloid therapy after considering the risks and benefits, **AND** who do not wish to know their brain amyloid status. ● Patients with obvious modifiable or temporary contributors that could account for their cognitive impairment (e.g., depression, medication, untreated sleep disorder, acute grief, thyroid disorder). Clinicians may wish to treat these modifiable contributors first and confirm that objective cognitive impairment persists before deciding whether to order a BBM test. ● Patients with limited life expectancy due to very advanced age, as the clinical significance and prognosis of brain amyloid are not well-defined in these populations. ● Patients with a history of conditions that may impact amyloid or phosphorylated tau in plasma in ways that have not been well-studied (e.g., neurocysticercosis, history of chemotherapy or radiation, chronic traumatic encephalopathy). ● Patients with other medical comorbidities or medications that interfere with levels of a given BBM (e.g., chronic kidney disease, ALS).

Footnotes:

*Comparison used for evidence synthesis: Any included BBM (index tests) vs Amyloid PET, CSF, or neuropathology (reference standards).

† A triaging test refers to a test in which a negative result rules out Alzheimer's disease with high probability, whereas a positive result should be confirmed using another method, such as CSF or amyloid PET biomarkers.

‡ Based on meta-analyses demonstrating a sensitivity of at least 90% and a specificity of at least 75%.

§ The panel acknowledges that the WashU %p-tau217 IP-MS test is not commercially available. It is very similar to the commercially available C2N %p-tau217 IP-MS test.

A confirmatory test refers to a test in which a negative test rules out Alzheimer's disease and a positive test confirms Alzheimer's disease with a high probability.

Based on meta-analyses demonstrating a sensitivity of at least 90% and a specificity of at least 90%.

Table 2. Legend for interpreting the certainty of the evidence and implementing strong vs. conditional recommendations

DEFINITION OF CERTAINTY OF THE EVIDENCE	
Category	**Definition**
High	Very confident that the true effect lies close to that of the estimate of the effect.
Moderate	Moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very Low	Very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

DEFINITION OF STRONG VS. CONDITIONAL RECOMMENDATIONS AND IMPLICATIONS FOR STAKEHOLDERS		
Implications	**Strong Recommendations**	**Conditional Recommendations**
For Patients	Most patients in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Most patients in this situation would want the suggested course of action, but many would not.
For Clinicians	Most patients should receive this course of action. Adherence to this recommendation, according to the guideline, could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping patients make decisions consistent with their values and preferences.
For Policy Makers	The recommendation can be adapted as policy in most situations.	Policy making will require substantial debate and the involvement of various stakeholders.

Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help to identify possible research gaps.

Sources: GRADE guidelines 3, GRADE guidelines 14, GRADE guidelines 15

------BELOW IS CONTEXTUAL INFORMATION FOR REFERENCE ONLY--------

Overview of project:

Background: In Spring 2024, the Alzheimer's Association convened a guideline panel of clinical and subject-matter experts to develop a regularly updated evidence-based clinical practice guideline on the use of blood-based biomarkers, a relevant need for aging and memory-care specialists. Once our methodological approach to this clinical topic matures to the desired state, we aim to make this a "living" guideline. In collaboration with systematic review and guideline methodologists, the guideline panel developed the scope, purpose, target audience, and clinical questions for this first iteration of the guideline; these details were shared at the Alzheimer's Association International Conference (AAIC) 2024 for public comment. Reviewers then used the finalized scope to conduct a systematic review of the best available evidence. In Spring 2025, the panel formulated draft evidence-based recommendations, now available for public comment, and are preparing manuscripts for submission to peer-reviewed journals.

Scope: The scope of this first iteration of the guideline focuses on individuals with objective cognitive impairment (including those with mild cognitive impairment (MCI) or dementia) who are undergoing evaluation for cognitive impairment in secondary or tertiary care settings. The recommendations do **not** apply to cognitively *unimpaired individuals* nor to *individuals in primary care settings*, however, future iterations will aim to address the use of BBM tests in these populations and settings.

At this stage, the panel has only considered individual biomarkers (including ratios that use a reference peptide as the denominator) rather than combinations of multiple biomarkers. Recommendations in this guideline apply to the use of a single biomarker cutoff. The decision to use a single biomarker cutoff was based on the availability of data at the outset of the project. The panel deliberately chose to focus on individual biomarkers initially, intending to evaluate combinations in subsequent phases. The panel is aware that combinations of biomarkers, such as the p-tau217/Aβ42 ratio or a fixed combination of Aβ42/Aβ40 and a p-tau217 ratio, are being commercialized and provided to clinicians. The panel also acknowledges the potential advantages of a two-cutoff approach to improve both positive and negative predictive values when using a test for diagnostic confirmation. As more evidence becomes available, the panel will consider certain biomarker combinations, as well as performance based on a two-cutoff approach.

Methodology: The Alzheimer's Association's methodological team followed the GRADE approach and the Cochrane Handbook for Diagnostic Test Accuracy to synthesize evidence (search conducted between January 2019- Nov 2024), assess the certainty of the evidence, move from evidence to decisions, draft recommendations, and assign the strength of recommendations. A priori panel decisions included: development of clinical questions in PICO format, included index tests and reference standards, statistical plan for meta-analysis, and clinical thresholds for decision-making. When discussing the body of evidence and drafting recommendations, the panel was blinded to all test names/brands by using placeholders (e.g., Test 1, Test 2, etc.). Methodologists managed conflicts of interest using predetermined rules set by the Alzheimer's Association to minimize bias.

Results or conclusion: The panel judged the benefits of using an *accurate* BBM test in the diagnostic workup of patients with cognitive impairment presenting to specialty care to outweigh the harms, and therefore made conditional recommendations for their use. Five BBM tests met the panel's predefined diagnostic test accuracy thresholds for triaging, one of which also met thresholds for confirmatory testing.

Next Steps: This clinical practice guideline (and associated systematic review) will be published in the next 3 months and will provide finalized recommendations based on the best available evidence published between 2019 and November 3, 2024. With the understanding that the field of BBM research is rapidly evolving, **these recommendations will be subject to frequent updating and may change based on the availability of new evidence.**

Additional information on systematic review and guideline methodology:

- Tests where current evidence was sufficient for decision-making by the panel and diagnostic test accuracy thresholds were met **(included in current recommendations in Table 1, subject to change with new evidence):**
    - %p-tau217
        - IP-MS, WashU
        - IP-MS Precivity™, C2N Diagnostics
    - p-tau217
        - IP-MS Precivity™, C2N Diagnostics
        - Immunoassay, Lumipulse, Fujirebio
    - Aβ42/40
        - HISCL, Sysmex

- Other tests that were analyzed but current evidence was insufficient for decision-making by the panel and/or did not meet diagnostic test accuracy thresholds *at the moment* **(not included in current recommendations in Table 1, do not preclude the possibility of recommending it in the future, as more data become available):**
    - Aβ42/40
        - Immunoprecipitation-Mass Spectrometry (IP-MS):
            - WashU
            - Amyloid MS™, Shimadzu
            - Precivity™, C2N Diagnostics

            - University of Gothenburg (UGOT)
        - High-performance liquid chromatography-differential mobility spectrometry-tandem mass spectrometry:
            - Araclon Biotech
        - Immunoassay:
            - Simoa, Quanterix 4plexE
            - Simoa, Quanterix single plexes
            - Simoa, Quanterix Neuro 3-plex A kit
            - Lumipulse™, Fujirebio
            - Elecsys™, Roche
    - p-tau181
        - Immunoassay:
            - Lilly assay, Meso Scale Discovery (MSD)
            - S-PLEX, MSD
            - Simoa, Quanterix p-Tau-181 Advantage Kit
            - Simoa, Quanterix 4plexE
            - Simoa, Quanterix UGOT
            - Lumipulse™, Fujirebio
            - Simoa, ADx Neurosciences
            - Elecsys™, Roche
    - p-tau231
        - Immunoassay:
            - Simoa, Quanterix UGOT
    - p-tau217
        - IP-MS:
            - WashU
        - Immunoassay:
            - Lilly assay, MSD
            - S-PLEX, MSD
            - Simoa, Quanterix Janssen
            - Simoa, ALZpath
            - Elecsys prototype, Roche (N-terminal)*
            - Elecsys prototype, Roche (mid-domain)*

* Discontinued. Not to be confused with Roche's latest p-tau217 assay, which has not been included in the meta-analysis.

Acceptable reference standards:

- Amyloid PET imaging (either visual read or quantitative cutoff)
- Cerebrospinal fluid analysis of Aβ42/40 or combinations of Aβ42 and p-tau (lumbar puncture)
- Neuropathology

Outcomes:

- Sensitivity
- Specificity
- If possible: PPV, NPV (was not calculable due to lack of consensus on prevalence of amyloid pathology)

- Patient-important outcomes and downstream consequences of using a blood-based biomarker test

A priori thresholds set by the panel for decision making:

The panel set decision thresholds a priori for triaging tests (90% sensitivity and 75% specificity) and confirmatory tests (90% sensitivity and 90% specificity). Borderline accurate tests were considered for inclusion in recommendations when one of the measures (sensitivity or specificity) was within 1-2% points of the corresponding decision threshold and the other measure far exceeded the corresponding decision threshold, and where sensitivity analyses indicated fragility of data and/or suboptimal analytical cutoffs. Note that all recommended tests were above the thresholds in the main or sensitivity analyses (that is, none were below any threshold).

Results of main analysis:

Forty-nine observational studies were identified that assessed the diagnostic test accuracy of the 31 BBM tests listed above in the population of interest. Youden's Index was the most common method for determining analytical cut-off in primary studies. Therefore, the main analysis is based on data that was derived using this method. Across all tests, pooled sensitivity ranged from 49-92%, and pooled specificity ranged from 53-97%. Overall certainty of the evidence ranged from moderate to very low. 5 tests met the pre-defined decision thresholds for triaging, one of which also met the thresholds for confirmatory testing (Table 3). Comprehensive results for all evaluated tests will be reported in the systematic review manuscript.

Table 3. Summary of findings for the 5 tests meeting pre-defined diagnostic test accuracy decision thresholds (90% sensitivity/75% specificity for triaging and/or 90% sensitivity and specificity for confirmatory testing).

Test Name	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	N studies (n participants)	Certainty of the Evidence using GRADE approach
%p-tau217 IP-MS (WASHU)	91.39% (88.19 - 93.79)	92.23% (88.67 - 94.74)	3 studies (4 cohorts) (1371)	Low*
%p-tau217 IP-MS (PrecivityTM)†	89.51% (86.67-91.79)	86.39% (82.12-89.77)	4 studies (2153)	Low*
p-tau217 IP-MS (Precivity™)	91.41% (86.64 - 94.58)	85.28% (78.31 - 90.29)	2 studies (775)	Low*

p-tau217 Lumipulse Immunoassay, Fujirebio ‡	89.02% (85.11 - 92.00)	89.06% (85.26 - 91.96)	5 studies (6 cohorts) (1173)	Low*
Aβ42/40 HISCL, Sysmex	90.08% (71.03 - 97.11)	83.25% (77.36 - 87.85)	1 study (2 cohorts) (397)	Low§

Footnotes:
*Rated down two levels due to serious issues of risk of bias and serious issues of imprecision.
† Sensitivity analysis with fixed specificity at 75.00% showed a sensitivity of 94.79%.
‡ Sensitivity analysis with fixed specificity at 75.00% showed a sensitivity of 94.47%.
§ Rated down two levels due to unclear issues of risk of bias and serious issues of imprecision.

Additional contextual factors considered as part of GRADE evidence-to-decision framework:

Additional contextual factors, using the GRADE approach, regarding the use of BBM tests (BBM vs. reference tests, but also, BBM vs. no testing) were considered. *We acknowledge this section is methodologically jargon-heavy, and will fully explain our methodology, the evidence, and our judgments on the evidence in our final manuscripts.*

Accurate BBM tests, when used in the clinical scenario described here (cognitively impaired patient seeking specialized care for their memory disorder), were judged to be associated with large desirable effects, small to moderate undesirable effects, possibly important uncertainty or variability in patients' values and preferences, moderate savings, probably increased equity, probable acceptability, and variable feasibility. Some users of this guideline may value these factors differently, which could impact decisions to implement recommendations at the clinical-, health system-, or policy-level.

Limitations of the evidence synthesis and evidence-to-decision process:

Eighty-four studies that would have otherwise met eligibility criteria were ultimately excluded due to cognitively impaired and unimpaired populations being analyzed together. We were therefore unable to parse out data on the population of interest. The panel made the a priori decision not to include such data because test performance could appear more favorable in populations with a bimodal distribution of brain amyloid (i.e., individuals with very low (cognitively unimpaired) or very high (AD-like dementia) brain amyloid levels).

Several studies did not report sufficient data to include in a meta-analysis (e.g., number of true positives, true negatives, false positives, and false negatives). These additional data were requested from the authors of all primary studies that did not report them, however, we only received these additional data from the authors for a portion of the requested primary studies. Studies not providing sufficient data were not included in meta-analyses and will be summarized narratively in the systematic review and clinical practice guideline manuscripts.

At the time of this systematic review, the vast majority of peer-reviewed evidence for individual BBMs presents sensitivity and specificity based on a single cut-point. However, because many plasma tests fall short of the accuracy required to confidently rule in or rule out the presence of brain amyloid with a single

cut-point, the field is rapidly moving toward alternate testing paradigms. One promising paradigm is the two cut-off approach, where values below a certain cut-point rule out brain amyloid and values above a certain cut-point rule in brain amyloid, while values in the middle require further testing with PET imaging or CSF. The panel will consider this approach in future guideline updates as additional evidence emerges.

Because new BBM tests are continually becoming available to clinicians, the panel decided not to limit eligibility criteria to tests that were commercially available at the time of this review. As a result, the data and recommendations include tests that may currently be commercially and not commercially available, including those that are clinically available, or for research use only.

Of the tests meeting diagnostic test accuracy thresholds, the certainty of the evidence was low. Reasons for low certainty of evidence for a given test included any combination of the following: serious issues of risk of bias, inconsistency of results across included studies, and imprecision within the estimates of sensitivity and specificity. As a result, the panel was only able to make conditional recommendations at this time. Interpretations and implications for conditional recommendations are provided in Table 2. Although the recommended tests may differ in performance, the panel has refrained from ranking them since the field is rapidly evolving, and adding new studies may likely result in modifications to any proposed rankings. Variations in cohort characteristics (e.g., selected research cohorts vs. real-world patient cohorts), plasma analysis design (e.g., single-batch vs. multiple batches analyzed prospectively over extended periods), and other factors may additionally explain some of the observed differences in test accuracy.

The full list of included studies and the list of excluded studies (with reasons for exclusion) will be provided in the final, published systematic review manuscript.

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Contact: *Please use the online form to provide feedback on this guideline. For any general questions about the Alzheimer's Association's Guideline Development Program, please contact Malavika Tampi, Director, Clinical Practice Guidelines Program and Methodology Lead (mptampi@alz.org).*

This particular document was prepared by the following guideline panel and methodology team members. Additional authors contributed to the systematic review and guideline manuscripts and will be appropriately included in publications along with conflict of interest disclosure forms for all.

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