ALZHEIMER'S ASSOCIATION | ALZPro

Alzheimer's Association® Clinical Practice Guideline: Integrating Blood-Based Biomarkers in Alzheimer's Disease Specialized Care

A Summary for Health Care Providers

This summary distills key recommendations from the full clinical practice guideline (CPG) and supports health care professionals (HCPs) in specialized care, such as neurologists, geriatricians, psychiatrists and memory clinic specialists, in appropriately considering and integrating these novel diagnostic tools in clinical practice.

This resource complements, but does not replace, the full BBM CPG. HCPs should consult the full **CPG document for complete guidance**.

The field of blood-based biomarkers (BBMs) for detecting Alzheimer's disease (AD) pathology is rapidly evolving. In addition to improving diagnostic accuracy for patients unable to access PET or lumbar puncture, BBMs are particularly important as new anti-amyloid-ß (Aß) therapies requiring biomarker confirmation of Aß pathology become increasingly available in clinical practice. These BBMs measure specific proteins and other substances in blood samples, such as forms of amyloid and tau, that can reflect core AD pathologies in the brain. They offer a less invasive and potentially more accessible means to assess these biological changes compared to traditional biomarker assessment methods like cerebrospinal fluid analysis or PET imaging, ultimately aiming to enhance the timeliness and accuracy of diagnosis and improve patient care pathways. To guide the effective clinical application of these tools, the Alzheimer's Association published its *Evidence-based Clinical Practice Guideline on the Use of Blood-based Biomarkers in the Diagnostic Workup of Alzheimer's Disease within Specialized Care* in July 2025.

Recommendations

Triage

Use a high-sensitivity BBM test during the diagnostic workup of AD to triage individuals with objective cognitive impairment.

Read more

Confirmatory

Use a high-sensitivity and high-specificity BBM test during the diagnostic workup of AD to confirm AD in patients with objective cognitive impairment.

Read more

Recommendations

Triage

Use a high-sensitivity BBM test during the diagnostic workup of AD to triage individuals with objective cognitive impairment.

In patients with objective cognitive impairment presenting to specialized memory-care settings, the panel suggests using a high-sensitivity BBM test as a triaging test in the diagnostic workup of Alzheimer's disease. A triaging test refers to a test in which a negative result rules out AD pathology with high probability, whereas a positive result should be confirmed using another method, such as CSF AD biomarkers or amyloid PET.

Recommendation Strength:

*Conditional recommendation, low certainty of evidence.**

What should you consider before using a BBM to triage?

A BBM test should not be considered before an appropriate cognitive evaluation by a healthcare professional, and test results should always be interpreted within the clinical context. To better support clinical decision-making, the panel urges HCPs to consider the pre-test probability of AD pathology for each patient when deciding whether to use a BBM test. A negative triaging test result suggests a lower likelihood of AD, while a positive result warrants confirmation with other methods.

What is the appropriate BBM test to use in triage?

BBM tests considered for triaging should demonstrate acceptable diagnostic accuracy, generally meeting or exceeding the panel's pre-defined thresholds (**at least 90% sensitivity and 75% specificity**) when compared to reference standards (amyloid PET, CSF, or neuropathology).

Confirmatory

Use a high-sensitivity and high-specificity BBM test during the diagnostic workup of AD to confirm AD in patients with objective cognitive impairment.

In patients with objective cognitive impairment presenting to specialized memory-care settings, the panel suggests using a high-sensitivity and high-specificity BBM test as a confirmatory test in the diagnostic workup of Alzheimer's disease. A confirmatory test refers to a test in which a negative test rules out AD pathology, and a positive test confirms AD pathology with a high probability.

Recommendation Strength:

*Conditional recommendation, low certainty of evidence.**

What is the appropriate BBM test to use to confirm AD?

BBM tests considered for confirming AD should demonstrate acceptable diagnostic accuracy, generally meeting or exceeding the panel's pre-defined thresholds such as (**at least 90% sensitivity and 90% specificity**) when compared to reference standards (amyloid PET, CSF, or neuropathology).

What if a BBM test meeting confirmatory thresholds is not available?

Currently, most single cut-off BBM tests do not meet pre-defined diagnostic accuracy thresholds for confirmation based on peer-reviewed evidence. Although some evaluated BBMs might qualify as confirmatory tests using a two-cut-off approach (where results between the cut-offs require gold-standard testing), the application of a two-cut-off approach was not assessed in this CPG.

The field of BBM technology is rapidly advancing. Future guideline updates will consider new evidence, including analytically validated BBM tests that meet confirmatory thresholds, possibly including different interpretive methods.

BBM tests may not be appropriate for individuals:

- Who are not candidates for, or have already made an informed decision against, anti-amyloid therapy AND who do not wish to know their brain amyloid status
- With obvious modifiable or temporary contributors that could account for their cognitive impairment
- With limited life expectancy, where the clinical significance of brain amyloid status is less clear
- Who have a history of conditions that may impact amyloid or phosphorylated tau in plasma in ways not yet well-studied
- With other medical comorbidities or medications known to interfere with the levels of a given BBM

*Based on last comprehensive literature search (January 2019-November 2024)

Considerations

Good Practice Statement

A BBM test should only be used following an appropriate clinical evaluation by a healthcare professional, and test results should always be interpreted within the clinical context. To better support clinical decision-making, the panel urges HCPs to consider the pre-test probability of AD pathology for each patient when deciding whether to use a BBM test.

Clinicians must be particularly cautious when ordering and interpreting triage tests for patients with a very low pre-test probability of Alzheimer's disease pathology. If a test with 75% specificity is used in this population, a sizable portion of positive results are likely to be false positives, necessitating confirmation with a gold-standard method (e.g., CSF analysis or amyloid PET).

What This Means in Practice

A conditional recommendation signifies that while a potential benefit exists, the decision to use a BBM test requires careful clinical judgment. Not all patients may benefit equally. Therefore, consider individuals' circumstances and values, and engage in a shared decision-making process. This is not a directive to use the test in every eligible patient.

A conditional recommendation signifies that while a potential benefit exists, the decision to use a BBM triaging test requires careful clinical judgment. The associated systematic review focused on tests evaluating single biomarkers and did not consider algorithms that combine BBMs with clinical variables such as age, sex, or *APOE* genotype. Not all patients may benefit equally. Therefore, consider individuals' circumstances and values, and engage in a shared decision-making process. This is not a directive to use the test in every eligible patient.

Conclusion

The Alzheimer's Association's clinical practice guideline marks an important step in integrating blood-based biomarkers into Alzheimer's disease diagnosis. This CPG supports the use of high-sensitivity BBMs as triaging tools in specialized care, while urging caution regarding their current use as standalone confirmatory tests with a single cut-off, emphasizing the need for interpretation within the full clinical context.

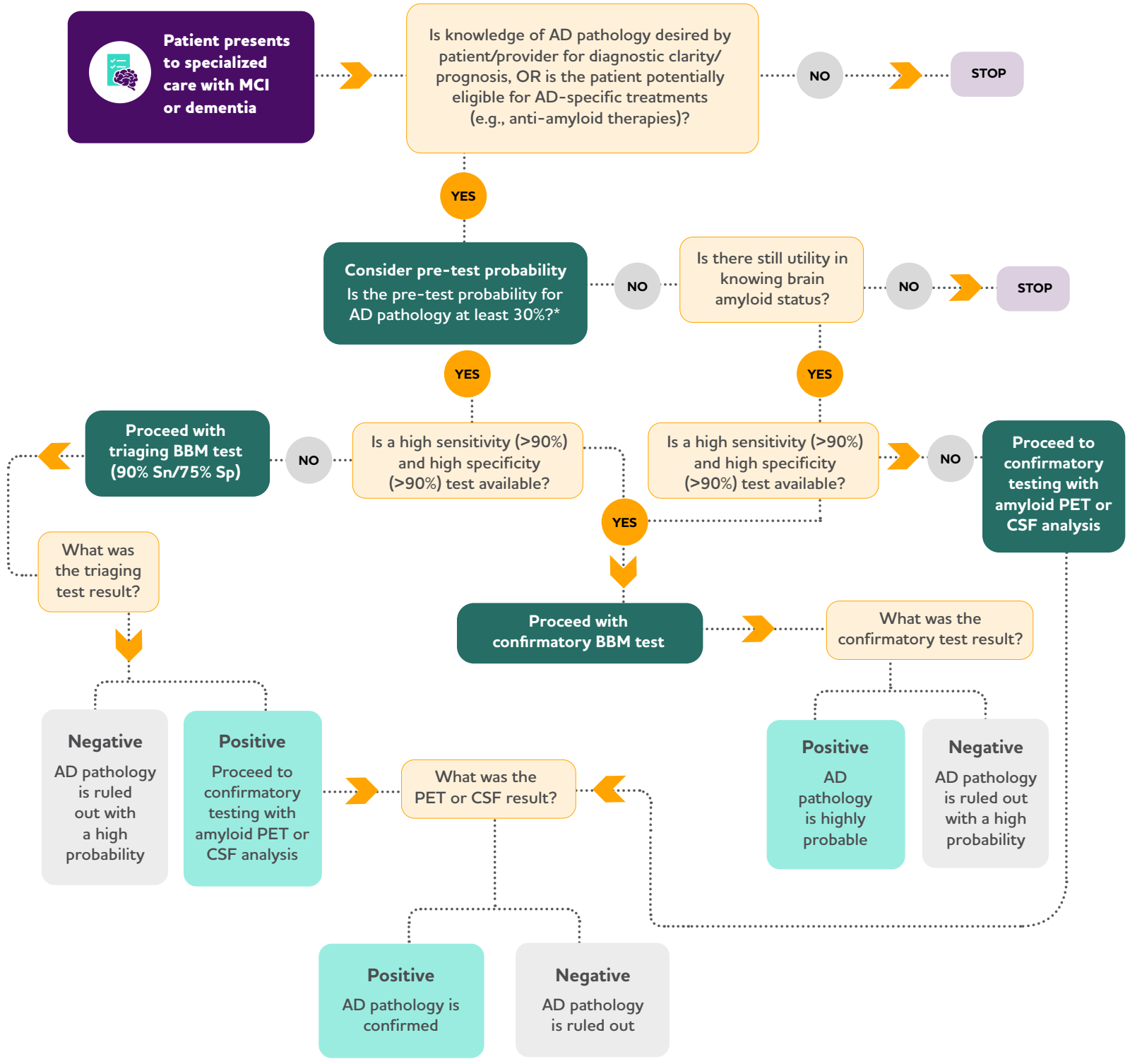
As "living guidelines," these recommendations will evolve with new evidence on BBM performance, diverse populations, and advanced analytical approaches. Health care professionals should consult the full CPG document for comprehensive guidance and stay informed of updates to effectively leverage these promising tools in the dynamic landscape of AD diagnosis.

View the latest evidence and updates to the BBM CPG at alz.org/BBMCPG

ALZHEIMER'S ASSOCIATION | ALZPro

For additional information and professional resources, visit **alz.org/ALZPro**.

Proposed Pathways for AD Biomarker Assessment in Specialized Care



*Pre-test probability is a subjective estimate based on available data and clinical judgment. With a pre-test probability of 30%, a test with 90% sensitivity and 75% specificity yields a positive predictive value (PPV) of approximately 61%. When the pre-test probability drops below 30%, the PPV declines toward or below 50%, meaning that a positive result becomes increasingly unreliable for detecting disease.

How Was the Clinical Practice Guideline Developed?

The Alzheimer's Association used a rigorous, evidence-based approach to develop the clinical practice guideline, including:

Expert Panel: A multidisciplinary panel of clinical and subject-matter experts developed clinical questions in PICO (Population, Intervention, Comparison, Outcome) format.

Systematic Review: The panel conducted a systematic review of peer-reviewed literature and meta-analysis of evidence from a comprehensive literature search (January 2019-November 2024), adhering to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and the Cochrane Handbook for Diagnostic Test Accuracy. The panel used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to determine the certainty of evidence and strength of recommendations, considering factors like benefits, harms, patient values and resource implications.

Pre-defined Thresholds: The panel established pre-defined diagnostic test accuracy thresholds for blood-based biomarkers for triaging and confirmatory purposes.

Blinded Review: The panel was blinded to specific test names/brands during the initial review of evidence and drafting of recommendations, focusing on performance characteristics. For the purpose of this guideline a BBM test is defined as the combination of a BBM (analyte) and the technology used to measure it (e.g., specific immunoassay or mass spectrometry method).

Limitations: The panel recognized limitations in the available evidence, such as study heterogeneity, lack of pre-test probability, disease prevalence and the predominance of data based on single cut-offs (interpreting results against one threshold), which influenced the recommendations.

Regulatory Considerations: The guideline is based on peer-reviewed evidence available at the time of the systematic review (ending November 2024). BBM tests, including those with regulatory approval, were only included if peer-reviewed studies meeting the panel's eligibility criteria were available at the time the systematic review period ended. The systematic review will be updated regularly and will continue to include studies meeting the panel's eligibility criteria.

Scope of Guideline

The BBM CPG applies to the use of a **single biomarker cut-off** for individuals:

- **Exhibiting objective cognitive impairment**, including mild cognitive impairment (MCI) or dementia
- Have confirmed cognitive impairment and are seeking evaluation in **secondary or tertiary specialized care settings**

The BBM CPG does not cover:

- Cognitively unimpaired individuals
- Individuals only evaluated in primary care settings
- The use of multiple biomarker combinations (beyond ratios that include a reference peptide)
- The use of two-cut-off approaches for BBM interpretation
- Regulatory status
- Step-by-step comprehensive care

Reference

Palmqvist S, Whitson HE, et al. Alzheimer's Association clinical practice guideline on the use of blood-based biomarkers in the diagnostic workup of suspected Alzheimer's disease within specialized care settings. *Alzheimers Dement 2025*; https://doi.org/10.1002/alz.70535.