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American Geriatrics Society Feedback – Use of Blood-based Biomarkers for Alzheimer's Disease in Specialty Care Settings Clinical Practice Guideline

The American Geriatrics Society (AGS) submitted these comments on May 19, 2025 in response to the Alzheimer's Association's (AA) Evidence-based Clinical Practice Guideline (CPG), planned for publication in July 2025, 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 (see Appendix on page 9 for draft AA CPG). On May 22, 2025, AGS submitted an addendum to its comment (see page 8).

AGS RESPONSE

AGS appreciates the opportunity to provide feedback on the recommendations within the Alzheimer's Association's (AA) evidence-based clinical practice guideline (CPG) on *Use of Blood-based Biomarkers for Alzheimer's Disease in Specialty Care Settings.*

Founded in 1942, AGS is a nationwide, not-for-profit society of geriatrics healthcare professionals dedicated to improving the health, independence, and quality of life of older people. Our 6,000+ members include geriatricians, geriatrics nurse practitioners, social workers, family practitioners, physician associates, pharmacists, and internists who are pioneers in advanced-illness care for older individuals, with a focus on championing interprofessional teams, eliciting personal care goals, and treating older people as whole persons. AGS is an anti-discriminatory organization. We believe in a society where we all are supported by and able to contribute to communities where ageism, ableism, classism, homophobia, racism, sexism, xenophobia, and other forms of bias and discrimination no longer impact healthcare access, quality, and outcomes for older adults and their care partners. AGS leads efforts to incorporate attention to older adults living with multiple chronic conditions into research[1,2] and clinical care[3,4] and is a champion for improving attention to the unique health care needs of older adults in workforce training.[5,6] We believe that understanding disease across the lifespan[7] is important to extending healthspan—the time someone lives in generally good health—for all of us as we age.

[1] Advancing Geriatrics Research: AGS/NIA Conference Series. American Geriatrics Society. Accessed May 16, 2025. https://www.americangeriatrics.org/programs/advancing-geriatrics-research-agsnia-conference-series
[2] The AGS/AGING Learning Collaborative. AGS CoCare. Accessed May 16, 2025. https://mccresearch.agscocare.org/what_is_the_ags_aging_learning_collaborative
[3] American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity. Guiding principles for the care of older adults with multimorbidity: an approach for clinicians. *J Am Geriatr Soc*. 2012;60(10):e1-e25. doi:10.1111/j.1532-5415.2012.04188.x
[4] McNabney MK, Green AR, Burke M, et al. Complexities of care: common components of models of care in geriatrics. *J Am Geriatr Soc*. 2022;70(7):1960–1972. doi:10.1111/jgs.17811
[5] American Geriatrics Society. Letters to House and Senate Appropriations Leadership on FY 2025 Funding for Geriatrics Workforce Training Programs. June 5, 2024. Accessed May 16, 2025. https://www.americangeriatrics.org/sites/default/files/Letters%20to%20House%20and%20Senate%20Appropriations%20Leadership%20on%20FY%202025%20Funding%20for%20Geriatrics%20Workforce%20Training%20Programs.pdf
[6] AGS Advancing Health Care in Surgical and Related Medical Specialties. Special Collection. *J Am Geriatr Soc*. Accessed May 16, 2025. https://agsjournals.onlinelibrary.wiley.com/hub/journal/15325415/agsadvancinggeriatrics
[7] Inclusion Across the Lifespan in Human Subjects Research. National Institutes of Health. Updated February 27, 2025. Accessed May 16, 2025. https://grants.nih.gov/policy-and-compliance/policy-topics/inclusion/lifespan

An important framework for how geriatrics health professionals care for older adults is the 5Ms of geriatrics health care.[8] Our members are on the frontlines of caring for older Americans, many of whom are living with multimorbidity, advanced illness, and/or with complicated biopsychosocial issues. The Geriatrics 5Ms informed the development of the 4Ms of age-friendly care (What **M**atters, **M**edications, **M**entation, and **M**obility) of the Age-Friendly Health Systems movement which seeks to reimagine the 21st century health system so as to provide care that is age-friendly, respects the goals and preferences of the older adult, and meaningfully and substantially includes the family caregiver in the plan of care.[9]

Below, we offer comments in response to the AA request for feedback on the draft recommendations that will be included in a planned CPG to be released later this summer on *Use of Blood-based Biomarkers for Alzheimer's Disease in Specialty Care Settings*.

GENERAL COMMENTS

We recommend that AA lead the guideline with a statement that defines clinical care as whole-person evaluation and management that respects a person's goals and preferences. Further, AA should define the patient population that this guideline is intended to support. AGS believes that this population is comprised of persons presenting with a degree of cognitive impairment that is consistent with mild cognitive impairment (MCI) or mild dementia and who are interested in pursuing amyloid-dependent therapy. It is also important for AA to consistently frame blood-based biomarker (BBM) testing as a tool that is available to clinicians who are clinically evaluating people presenting with cognitive complaints and that the results should always be interpreted within the clinical context.

<u>Definition of Specialty Care</u>

If not already spelled out in the CPG, we recommend that AA provide a definition of specialty care setting. Specifically, it would be important for clinicians to know which of the "specialty care settings" are applicable for the guideline. In its prior work, AA has used the following examples of specialties involved in treating Alzheimer's disease (AD) and AD and related dementias (ADRD): geriatrics, psychiatry, neurology, and neuropsychology.[10] AA has also referenced subspecialty care settings, indicating that this is usually behavioral or geriatric neurology, geriatric or neuropsychiatry, or geriatrics.[11]

<u>Recommended Additional Comment Period</u>

As a general comment, providing the recommendations without the full text of the proposed CPG made it difficult to review and provide meaningful comments on these proposed recommendations. The document shared for review lacks the explanation of the panel's rationale for each recommendation and does not include information on the evidence that was reviewed to arrive at these recommendations. As an example, it would be helpful for reviewers to understand how Table 2 was utilized in practice and

[8] Tinetti M, Huang A, Molnar F. The Geriatrics 5M's: A new way of communicating what we do. *J Am Geriatr Soc*. 2017;65(9):2115. doi:10.1111/jgs.14979

[9] Mate KS, Berman A, Laderman M, Kabcenell A, Fulmer T. Creating age-friendly health systems - a vision for better care of older adults. *Healthc*. 2018;6(1):4-6. doi:10.1016/j.hjdsi.2017.05.005

[10] Atri A, Dickerson BC, Clevenger C, et al. DETeCD-ADRD: The Alzheimer's Association Clinical Practice Guideline for the Diagnostic Evaluation, Testing, Counseling and Disclosure of Suspected Alzheimer's Disease and Related Disorders: Comprehensive Report. December 2024. Accessed May 19, 2025. https://www.dropbox.com/scl/fi/tcbfvkzkac36cfiox1q72/DETeCD-ADRD-CPG-Comprehensive-Report.pdf

[11] Atri A, Dickerson BC, Clevenger C, et al. Alzheimer's Association clinical practice guideline for the diagnostic evaluation, testing, counseling, and disclosure of suspected Alzheimer's disease and related disorders (DETeCD-ADRD): executive summary of recommendations for primary care. *Alzheimers Dement.* Published online December 23, 2024. doi:10.1002/alz.14333

what the cut point was for determining whether the strength of the evidence supported a strong or conditional recommendation.

We recommend that AA provide a second, longer, open comment period for the full text of the proposed CPG. This would provide more transparency on the content of the guideline and allow reviewers a more meaningful opportunity to provide input into this first-ever guideline on the use of BBMs in clinical practice. Doing so would be in alignment with best practice recommendations from the Institute of Medicine of the National Academies of Science as outlined in "Clinical Practice Guidelines We Can Trust" and the Council of Medical Specialty Societies, "CMSS Principles for the Development of Specialty Society Clinical Practice Guidelines" on guideline development. In addition to the panel members' conflicts of interest that will be included in publications, it would be important to also include the process by which these were resolved. Given that the Association is a recipient of pharmaceutical industry funding, we encourage the panel to describe the policies and procedures in place at AA that are focused on ensuring that the development of the guideline was developed independently from AA's corporate supporters and industry partners.

COMMENTS ON RECOMMENDATIONS 1 AND 2

Consistent with our general comment above, we recommend, based on available evidence, that the guideline consistently recognize and frame the limited role of BBMs in clinical care which is to help identify candidates diagnosed with MCI or mild dementia who may benefit from amyloid beta targeting AD-specific treatments.[12,13] Further, for each recommendation, it is important that AA define when a BBM test is appropriate and consistently convey that a BBM test in clinical care:

1. Is a tool that is available to health professionals who are clinically evaluating someone presenting with cognitive impairment **and** who is interested in pursuing anti-amyloid therapy for AD.
2. Test results should always be interpreted within the clinical context of that person, taking into account other health conditions, including what matters most to that individual.

Clinical Scenarios Where BBM Might Not be Appropriate

We appreciate the inclusion of clinical scenarios where a BBM test may not be appropriate. It is difficult to assess these statements in the absence of references, rationale, and other contextual comments that will be included in the final manuscript.

AGS recommendations for specific clinical scenarios are:

Scenario: *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.*

- It would be important for AA to identify where the decision about administering a BBM would occur in the clinical workflow.
- AGS recognizes that there may be individuals who want to know their brain amyloid status despite a lack of apparent clinical decision that would follow undergoing a BBM test. For these

[12] Bun S, Ito D, Tezuka T, et al. Performance of plasma Aβ42/40, measured using a fully automated immunoassay, across a broad patient population in identifying amyloid status. *Alzheimers Res Ther.* 2023;15(149):1-12. doi:10.1186/s13195-023-01296-5

[13] Widera E, Covinsky K. The limited role of Alzheimer disease blood-based biomarkers in primary care. *JAMA Intern Med.* Published online: May 12, 2025. doi:10.1001/jamainternmed.2025.0976

individuals, it would be important for AA to include information on the value of such testing in a person without cognitive impairment given that many biomarker-positive people will not go on to develop AD.[14,15,16,17]

Scenario: *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.*

- Given the heterogeneity of aging and of older adults, we believe that the scenario for patients with limited life expectancy should be expanded to address other relevant characteristics that should be considered when making this decision. In general, the Society believes that decision-making needs to be individualized to the specific circumstances of an older adult and age alone should not be used as the sole criteria for decision-making about testing and treatment.[18,19]

Scenario: *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).*

- AA should consider deleting "neurocysticercosis" given how rare this disease is.

We encourage AA to include clinical scenarios in which BBMs may not be appropriate in any collateral materials that are being developed (e.g., implementation guidance for clinicians, public education resources). For the public, it is critically important that educational materials are clear that there is currently no evidence to support obtaining a BBM test in the absence of clinical symptoms of objective cognitive impairment and a person's intent to pursue anti-amyloid therapy.

ADDING A THIRD RECOMMENDATION

AGS appreciates that the scope of this guideline makes it clear that it is not intended for use in primary care practice nor applicable to individuals without objective cognitive impairment. We strongly recommend that AA create a third recommendation along the lines of the following:

- This guideline is not intended for use in primary care, nor do we recommend that an asymptomatic individual, defined as someone showing no signs of objective cognitive impairment, undergo blood-based biomarker testing.

[14] Brookmeyer R, Abdalla N. Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease. *Alzheimer's Dement*. 2018;14(8):981-988. doi:10.1016/j.jalz.2018.03.005

[15] Roberts RO, Aakre JA, Kremers WK, et al. Prevalence and outcomes of amyloid positivity among persons without dementia in a longitudinal, population-based setting. *JAMA Neurol*. 2018;75(8):970-979. doi:10.1001/jamaneurol.2018.0629

[16] Jansen WJ, Janssen O, Tijims BM, et al. Prevalence estimates of amyloid abnormality across the Alzheimer disease clinical spectrum. *JAMA Neurol.* 2022;79(3):228-243. doi:10.1001/jamaneurol.2021.5216

[17] Erickson P, Simrén J, Brum WS, et al. Prevalence and clinical implications of a β-amyloid–negative, tau-positive cerebrospinal fluid biomarker profile in Alzheimer disease. *JAMA Neurol.* 2023;80(9):969-979. doi:10.1001/jamaneurol.2023.2338

[18] Farrell TW, Ferrante LE, Brown T, et al. AGS position statement: resource allocation strategies and age-related considerations in the covid-19 era and beyond. *J Am Geriatr Soc.* 2020;68(6):1136-1142. doi:10.1111/jgs.16537

[19] Farrell TW, Francis L, Brown T, et al. Rationing limited healthcare resources in the covid-19 era and beyond: ethical considerations regarding older adults. *J Am Geriatr Soc.* 2020;68(6):1143-1149. doi:10.1111/jgs.16539

The reality is that the currently available evidence does not support use of BBMs, such as the Washington University (WashU) developed %p-tau 217 IP-MS test,[20] in primary care settings[13] and research to date has mainly focused on individuals across the AD continuum.[21,22]

Additionally, there is no current evidence that discovery of biomarker positivity across diverse populations without clinical symptoms should lead to initiation of specific clinical interventions. Much remains to be learned about how biomarkers perform as true indicators of specific brain pathologies across different clinical populations, including those with various comorbid conditions,[23] before implementation into routine clinical care. Considering the racial and ethnic disparities in the prevalence of AD and ADRD among the subpopulations and increasing diversity among older people, it is crucial to determine whether age, gender, and racial and ethnic representation in the data is sufficient to support generalizability.[24] The existing disparities in access to AD diagnosis and care must not be exacerbated by evidence based on non-representative participant populations. It would also be critically important to understand the impact of biomarker-based diagnosis on different populations as well as any potential or unintended harms in diagnosis and care, particularly for historically minoritized populations that have been disproportionately affected by the disease and disproportionately understudied and underdiagnosed. We recommend explicitly calling out the critical need for the inclusion of underrepresented groups in clinical trials as well as validation studies of BBM.

We strongly encourage the AA to take into consideration the external environment within which this guideline is being released given pharmaceutical industry investments in marketing the newer monoclonal antibodies (mAbs). As an example, Eli Lilly has created a website targeted to the public, Don't Wait While Memory and Thinking Issues Pile Up | More Than Normal Aging and another website for clinicians to promote early diagnosis of AD, Biomarker Evidence for Assessing Alzheimer's Disease | Diagnostic Workup. There are corresponding advertising campaigns across traditional media that are focused on the concept of "more than normal aging."

SPECIFIC COMMENTS

Clinical Question 1 & Recommendation Statement 1

The first clinical question and recommendation statement in Table 1 are conflicting. The question asks about individuals "seeking specialized care for cognitive disorders" whereas the statement intended to address the question refers to patients "presenting to specialized memory-care settings." If read alone, the clinical question may be interpreted as whether BBMs are appropriate before an individual is seen by specialty care as part of the referral process or as a "triage" tool to get into specialty care, a very different question than the scope of the document which is CPGs for use of BBMs within specialty care. Furthermore, "presenting" may be interpreted as an event that takes place after a referral to a specialty provider but before an appropriate clinical evaluation has been performed by the specialty provider. AGS recommends rewording the clinical question and recommendation using specific and clearer terms

[20] Barthélemy NR, Salvadó G, Schindler SE, et al. Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests. *Nat Med.* 2024;30(4):1085-1095. doi:10.1038/s41591-024-02869-z

[21] Antonioni A, Raho EM, Di Lorenzo F, et al. Blood phosphorylated tau217 distinguishes amyloid-positive from amyloid-negative subjects in the Alzheimer's disease continuum. A systematic review and meta-analysis. *J Neurol.* 2025;272(252):1-16. doi:10.1007/s00415-025-12996-3

[22] Dyer AH, Dunne J, Dolphin H, et al. Clinical performance of the fully automated Lumipulse plasma p-tau217 assay in mild cognitive impairment and mild dementia. *Alzheimers Dement (Amst)*. 2025;17(1):e70080. doi:10.1002/dad2.70080

[23] Mielke MM, Dage JL, Frank RD, et al. Performance of plasma phosphorylated tau 181 and 217 in the community. *Nat Med.* 2022;28:1398-1405. doi:10.1038/s41591-022-01822-2

[24] Matthews KA, Xu W, Gaglioti AH, et al. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged ≥65 years. *Alzheimers Dement.* 2019;15(1):17-24. doi:10.1016/j.jalz.2018.06.3063

that align with the scope of the paper (how BBM should be used within specialty care) and the remarks section that BBMs alone do not substitute for an appropriate clinical evaluation by a healthcare professional.

The term "triaging" should also be reconsidered as it is not appropriate in the context of this CPG. The footnotes include a description of triaging test as "a test in which a negative result rules out AD with high probability, whereas a positive result should be confirmed using another method, such as CSF or amyloid PET biomarkers." This footnote describes a two-step diagnostic workup for the presence of amyloid in the brain after an initial workup is done in a specialty clinic. This is different than the more general understanding of "triage," which is a process for quick assessment of a patient for further workup or treatment. Given this, the term "triaging" may lead to confusion and assumptions that this guideline is referring to using BBM to "triage" patients to a memory specialist for further workup and treatment or that the specialty clinic should use this in deciding who receives an appropriate clinical evaluation. AGS strongly encourages avoiding the term "triage" altogether.

In addition, BBM as described in Table 1 would be used to support identification of AD pathobiology, which may satisfy an individual's desire to be aware of pathobiology and/or help qualify an individual for treatment with anti-amyloid mAbs. Considering the fluidity of the evidence base in the field, it may be outside the scope of this guideline in recommending whether a positive BBM test should be followed with cerebrospinal fluid (CSF) or PET verification absent a person's intent to pursue mAbs therapy. AGS also believes that when identifying potential candidates for anti-amyloid mAbs, the specialty setting's capability to administer the mAbs should be explicitly stated or the expectation should be clear for pre-qualification testing when making referrals.

Clinical Question 2 & Recommendation Statement 2

Recommendation Statement 2 indicates that WashU %p-tau 217 IP-MS, can be used as a standalone diagnostic tool while Recommendation Statement 1 also identifies the WashU %p-tau 217 IP-MS as a triaging test (see earlier comments on the use of the term "triage"). AGS encourages providing clarification on the tool's applicability to both determining what next steps should be for an individual patient and diagnosing a patient. If it is a tool for standalone diagnostics, it does not need triaging by the very definition of standalone diagnostic. Further, it is critical to understand the differentiation between MCI subtypes prior to ordering blood p-tau 217 tests as amyloid prevalence varies across the cognitive phenotypes and a comprehensive assessment should be performed to prevent misdiagnoses.[25] While the recommendations do not appear to suggest conducting a biomarker test before a comprehensive assessment, we encourage explicit expression of AA's perspective on this topic as the intent of the document is to guide and support clinicians in practice in the diagnosis and treatment of people who may be living with AD.

Given the focus on clinical practice, we are concerned that the WashU %p-tau 217 IP-MS test is out of scope for the guideline and premature to recommend as a diagnostic tool due to its commercial unavailability. The footnote to this recommendation seems to suggest that practicing clinicians can substitute the commercially available C2N %p-tau 217 IP-MS test for the WashU %p-tau 217 IP-MS test. If that is the case, we recommend including the data that supports this suggestion and the rationale for excluding the C2N %p-tau 217 IP-MS test from Recommendation Statement 2 as a confirmatory tool. If that is not what the panel intends to suggest with this footnote, AGS suggests rephrasing or removing the recommendation until such time as there is a commercially available BBM with evidence supporting a recommendation for use as a confirmatory tool in clinical practice. While the C2N %p-tau 217 IP-MS is

[25] Bouteloup V, Villain N, Vidal JS, et al. Cognitive phenotyping and interpretation of Alzheimer blood biomarkers. *JAMA Neurol.* 2025;82(5):506-515. doi:10.1001/jamaneurol.2025.0142

one of the BBM tests that are commercially available, this is a rapidly evolving landscape. Further, there is only one BBM (Lumipulse G pTau217/ß-Amyloid 1-42 Plasma Ratio) that has received market clearance from the Food and Drug Administration (FDA) which means that these tests are, generally, not currently paid for by public or private insurers. Although AA intends to update this CPG frequently, we recommend caution in making a recommendation for a single specific test that is not commercially available and encourage AA to include a discussion of the economic implications for patients of these recommendations.

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

While there was no specific request for comments on Table 2, AGS believes that the guideline should include recognition that the framework is adapted from the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Handbook and provide a rationale for use of an adapted version of GRADE.

In making these comments, AGS understands the heavy toll of AD on patients, caregivers, and their families and we are pleased to see advances in technologies for diagnosis, efforts to pinpoint the molecular mechanisms that underlie dementing illnesses, and more attention to how exposome influences brain health in ways that often lead to health disparities in AD and ADRD. It is important at this juncture to recognize that the evidence supporting implementation of BBM diagnosis more broadly is weak while at the same time beginning to educate practicing clinicians and the public about these new technologies. Specifically, now is the time to implement public and professional education efforts that prepare society that some people may be diagnosed with AD yet never live to develop objective evidence of cognitive impairment or progress to meet clinical criteria for dementia.

Significant evidence now supports recommendations that cancer screening and treatment should not be applied uniformly in all populations; in contrast, we do not have the evidence to guide how BBM diagnosis of AD should be handled in all clinical populations in different settings, particularly primary care. AGS prioritizes what matters most to patients, their families, and other care partners as well as consideration of the whole person. Until more compelling evidence emerges on BBMs, we urge careful consideration and thoughtful review of the CPG as you move through the development process.

Thank you for taking the time to review our feedback and recommendations. For additional information or if you have any questions, please do not hesitate to reach out.

ADDENDUM TO AGS 5/19/2025 COMMENTS

This is an addendum to comments submitted by the American Geriatrics Society (AGS) on May 19, 2025, in response to the Alzheimer's Association request for input on the Use of Blood-based Biomarkers for Alzheimer's Disease in Specialty Care Settings Clinical Practice Guideline Recommendations and Remarks.

AGS would like to add this recommendation for a modification to the Clinical Scenarios Where BBM Might Not be Appropriate to its prior comments.[1]

Scenario: *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.*

Considering that BBMs inform diagnosis of AD and patients' candidacy for or decision against anti-amyloid therapy would not affect decision-making to seek diagnosis, we recommend the following edit to this scenario:

- *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.*

[1] This addendum was submitted outside of the comment period on May 22, 2025.

APPENDIX

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 (PrecivityTM)	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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