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POLICY FORUM

Considerations for widespread implementation of blood-based biomarkers of Alzheimer's disease

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Abstract

Diagnosing Alzheimer's disease (AD) poses significant challenges to health care, often resulting in delayed or inadequate patient care. The clinical integration of blood-based biomarkers (BBMs) for AD holds promise in enabling early detection of pathology and timely intervention. However, several critical considerations, such as the lack of consistent guidelines for assessing cognition, limited understanding of BBM test characteristics, insufficient evidence on BBM performance across diverse populations, and the ethical management of test results, must be addressed for widespread clinical implementation of BBMs in the United States. The Global CEO Initiative on Alzheimer's Disease BBM Workgroup convened to address these challenges and provide recommendations that underscore the importance of evidence-based guidelines, improved training for health-care professionals, patient empowerment through informed decision making, and the necessity of community-based studies to understand BBM performance in real-world populations. Multi-stakeholder engagement is essential to implement these recommendations and ensure credible guidance and education are accessible to all stakeholders.

KEYWORDS

Alzheimer's disease, amyloid, biomarker, blood-based biomarkers, clinical implementation, clinical practice, cognitive impairment, disease-modifying treatment, ethics, patient journey, primary care, secondary care

1 | INTRODUCTION

Alzheimer's disease (AD), the most common cause of dementia, is characterized by the accumulation of amyloid beta (Aβ) proteins, hyperphosphorylated tau protein, and neurodegeneration in brain regions critical for cognitive function.[1] AD pathology can precede cognitive symptoms by decades.[2] As the disease advances to the symptomatic phase, individuals initially experience mild cognitive impairment (MCI) before transitioning to AD dementia. In the United States, approximately one in nine people over the age of 65 are living with AD.[3]

Symptomatic AD is diagnosed by a range of health-care professionals (HCPs), including primary care providers (PCPs); nurse practitioners; physician assistants; and specialists such as neurologists, geriatricians, and geriatric psychiatrists.[3] Most diagnoses are made by non-specialists, predominantly PCPs, due to the limited number of dementia specialists.[4–6] However, diagnosing and managing symptomatic AD is known to be challenging, fueling concerns that HCPs lack the necessary resources to manage the increasing number of patients seeking care.[7–9] This concern is compounded by the severe shortage of dementia specialists, with projections indicating a deficit in neurologists across all US regions by 2025.[6]

Even after a comprehensive evaluation, access to appropriate care is limited given the high prevalence of misdiagnosis. It has been reported that up to 92% of patients with MCI remain undiagnosed or misdiagnosed in primary care, and ≈ 25% to 30% of symptomatic AD cases are misdiagnosed at secondary dementia clinics.[10,11] Misdiagnosis, especially common in the early stages when symptoms are subtle, often leads to delays in care or inappropriate treatment.

Biomarker testing for AD pathology typically involves positron emission tomography (PET) with an amyloid-binding radiotracer and/or assays to measure concentrations of amyloid and tau proteins in cerebrospinal fluid (CSF).[12] However, clinical use of these tools is restricted due to cost, insurance coverage and out-of-pocket expenses, limited accessibility outside of specialty care settings, and perceived invasiveness.[10,12,13] Blood-based biomarker (BBM) tests offer a promising alternative to these traditional biomarker modalities. Blood collection, being less invasive and widely available, makes BBM tests for AD pathology more feasible compared to PET scans and lumbar punctures to collect CSF. Additionally, BBM tests are more accessible to non-specialists and can be rapidly scaled up to address the growing number of AD cases amidst a shortage of dementia specialists. Furthermore, with the emergence of disease-modifying treatments (DMTs) necessitating confirmation of amyloid pathology, AD biomarker testing becomes increasingly crucial in assessing patients with cognitive impairment, underscoring the demand for a scalable biomarker tool.[14,15]

While BBM tests have been widely used in AD research studies and clinical trials,[10,12,13,16] several important considerations must be addressed for their widespread implementation in clinical practice. Here we discuss key considerations for the clinical adoption of BBMs for AD from The Global CEO Initiative (CEOi) on Alzheimer's Disease BBM Workgroup.

RESEARCH IN CONTEXT

1. **Systematic review**: Experts in Alzheimer's disease (AD) biomarkers and clinical management of AD convened to discuss barriers to implementing AD blood-based biomarkers (BBMs) in primary and secondary care settings and the ethical implications of these tests. Following expert deliberation and input from diverse stakeholder groups, challenges and recommendations for widespread clinical implementation of AD BBMs were identified.
2. **Interpretation**: Lack of consistent recommendations for assessing cognitive impairment, need for education on BBM test characteristics, insufficient evidence on BBM performance in diverse populations, and ethical considerations surrounding patients' right to decide whether to undergo BBM testing and confidentiality were identified as key challenges to BBM clinical adoption.
3. **Future directions**: Evidence-based guidelines for cognitive assessment; tailored training for health-care professionals; and comprehensive patient resources on the use, interpretation, and implications of BBM tests are needed for the widespread implementation of BBMs in clinical practice.

2 | METHODS

CEOi, under the auspices of UsAgainstAlzheimer's, initiated the BBM Workgroup in 2022 to prepare stakeholders for the widespread adoption of BBM tests in clinical practice to enable a simpler, more timely, and accurate diagnostic experience for patients with symptomatic AD in the United States.[17] The objectives of the BBM Workgroup were to define minimum acceptable performance standards for BBM tests and provide recommendations for implementing BBMs in clinical practice. A workstream was established for each objective. Minimum performance standards and clinical implementation pathways have been previously published.[18,19]

In addition to developing clinical implementation recommendations, this workstream identified several critical considerations for implementing BBMs into clinical practice. These considerations are discussed in detail in this publication, as a companion piece to Mielke et al., 2024 under review for publication. Full details on the methods for forming the workgroup and generating consensus recommendations can be found in Mielke et al. 2024, under review for publication.

In brief, co-leaders (M.M.M. and C.U.) and a core team of diverse experts in biomarker testing and clinical management of AD (M.M.M., C.U., M.A., J.W.A., A.J., P.J.L., A.R., J.T., D.W.) conducted a literature review to identify barriers, facilitators, and ethical considerations for implementing AD BBM tests in primary and secondary care settings. Topics from the literature were prioritized based on their alignment with the objectives and scope of the workgroup. These topics were

then analyzed and discussed extensively among the core team. Key considerations and consensus recommendations to address the issues posed by these considerations were drafted by the core team and presented to the BBM Workgroup for feedback.

3 | CONSIDERATIONS FOR WIDESPREAD IMPLEMENTATION OF AD BBMS

3.1 | Lack of consistent recommendations for assessment of cognitive impairment in primary care is a barrier to BBM adoption

Timely detection of cognitive impairment in primary care is necessary to facilitate access to BBMs for AD. However, cognitive testing is not routinely conducted for many older adults in primary care.[20,21] This is largely due to the lack of consistent guidelines recommending annual cognitive screening, inadequate training among PCPs in administering and interpreting neurocognitive evaluations, limited time PCPs have with patients to conduct screening in the context of managing multiple chronic conditions, and the lack of awareness on the importance of early detection.[22] Additionally, Medicare offers limited guidance on cognitive assessments beyond mention of using a "validated structured assessment tool."[23] Strikingly, more than half of Medicare beneficiaries aged ≥ 65 are unaware that cognitive screening is offered free of charge during the Medicare Annual Wellness Visit, and less than a third report undergoing a structured cognitive assessment.[24,25] Moreover, even when offered, many patients decline cognitive testing due to stigma or other concerns.

To address the current unmet needs that limit cognitive testing in primary care, the BBM Workgroup recommends several measures. These include the development of evidence-based guidelines for population-based screening of MCI, the creation of electronic health record algorithms to identify individuals at high risk, significant training programs to help HCPs identify subtle cognitive decline, and improved reimbursement for the time spent assessing cognition by HCPs. Implementing these initiatives would help address the barrier imposed by the severe shortage of dementia specialists, as well as significantly reduce wait times for specialist visits.[26,5] In addition, the workgroup is aligned with the EU/US Clinical Trials in Alzheimer's Disease Task Force recommendation to embrace digital cognitive assessments for wider accessibility, including advances that allow for remote collection and assessment of cognitive outcomes.[27] However, a comprehensive discussion on the implications of implementing these digital tools is beyond the scope of this work.

Various solutions have been proposed to promote cognitive screening during the Medicare Annual Wellness Visit, such as setting national benchmarks for improvement, enhancing provider reimbursement, and training other staff members to conduct evaluations to alleviate the burden on PCPs.[28,29] To raise public awareness of the importance of early cognitive screening, initiatives like the "Go Annual" campaign in Georgia can be implemented to encourage the general public to take advantage of their free visit to discuss undergoing a cognitive assessment with their clinician.[30]

3.2 | HCP education is needed to determine the predictive value of BBM tests across patient populations

When interpreting BBM test results, it is critical to consider the positive and negative predictive values (PPV and NPV) of a test. PPV is the likelihood that a patient with a positive BBM test will also test positive with a validated reference standard, whereas NPV represents the likelihood that a patient with a negative BBM test will test negative with a validated reference standard. These values are driven by the prevalence of pathology for the intended context of use. Therefore, accurately estimating the appropriate prevalence is essential for interpreting BBM test results, and many HCPs may require guidance in doing so.

To address this need, the BBM Workgroup recommends developing educational programs that build confidence among HCPs in selecting the appropriate prevalence of AD pathology and calculating the PPV and NPV for BBM tests. Additionally, such education must be integrated into medical training programs to ensure that HCPs caring for older adults are proficient in accurately interpreting the predictive value of AD BBM tests. An online calculator that enables HCPs to visualize the relationships among PPV, NPV, test performance (sensitivity and specificity), and the prevalence of amyloid pathology is already available for dissemination: https://amyloid.shinyapps.io/NPV_PPV/.

Moreover, many BBM tests are likely to adopt a two-cut-off approach, classifying patients as positive, intermediate, or negative. This is, in part, because ≈ 5% to 20% of individuals have intermediate AD biomarker values near the cut-off, leading to potential discordant results upon repeat testing.[31–33] Identifying patients with intermediate biomarker values enhances overall test accuracy for individuals with positive or negative results. However, for some immunoassays, the intermediate zone has been reported to be ≥ 30%, which diminishes the utility of the assay. It is unclear whether these patients should undergo a second biomarker test with a different modality (e.g., amyloid PET or CSF) or receive a second BBM test at a later time.[16,31,33] Developing consensus recommendations for managing patients with intermediate biomarker values should be considered.

3.3 | Interpreting BBM test results in diverse populations is limited by lack of substantial evidence

Studies of BBM tests for AD have primarily been conducted in well-characterized, homogenous populations.[34] However, real-world patients demonstrate significant heterogeneity.[34–38] Several comorbidities, such as chronic kidney disease, a history of myocardial infarction, stroke, and obesity, have been found to influence AD BBMs; however, there are currently no established guidelines for interpreting BBM tests in patients with multiple chronic conditions.[39] The lack

of consideration for these comorbidities when interpreting BBM levels may result in misdiagnoses.

One potential approach to mitigate the impact of comorbidities on biomarker levels is the use of biomarker ratios, such as the Aβ 42/40 ratio or the ratio of phosphorylated to non-phosphorylated plasma tau.[40,41] Moreover, racial, ethnic, and geographical differences have been observed to affect AD-related CSF biomarkers and amyloid PET mean values.[42–44] However, it remains unclear whether similar differences exist for plasma BBMs or if any disparities due to variations in chronic condition prevalence among different demographic groups or other social determinants of health exist.

Evidence from large community-based studies encompassing older adults from diverse backgrounds, including those with multiple chronic conditions, is crucial for accurately interpreting BBM test results across diverse populations and will allow for further exploration of the utility of BBM ratios. The BBM Workgroup advocates for the implementation of such studies and endorses the recommendation by Langbaum et al. to establish a centralized database to aid clinicians in identifying appropriate phenotypes across diverse populations.[45] Leveraging datasets like All of Us, led by the National Institutes of Health, can facilitate the inclusion of diverse representation in future studies.[46]

3.4 | Implications of future direct-to-consumer BBM tests

The imminent availability of direct-to-consumer (DTC) BBM tests raises important considerations regarding their integration into the patient care pathway for diagnosing AD. First, these tests should meet the minimum performance standards previously established by the BBM Workgroup for the intended context of use.[18] Such tests may appeal to some patients because they allow for autonomy, especially if there are concerns about the test result being incorporated into their medical record. Conversely, a poorly performing DTC BBM test would likely cause significant distress by providing inaccurate information such as falsely detecting amyloid positivity, and create bottlenecks in future care, particularly if used by individuals without cognitive symptoms.

Furthermore, a BBM test should not be used in isolation to diagnose AD but as part of a comprehensive evaluation of the patient's overall presentation (Mielke et al., 2024, under review for publication). The BBM Workgroup recommends that DTC BBM tests include a disclaimer stating the necessity of consulting an HCP for interpretation and discussion of the results within the broader context of clinical assessment. Education will be needed to help HCPs interpret DTC BBM test results and discuss the results with their patients. Moreover, patients should be educated about the importance of having their DTC test results evaluated by an HCP and the potential implications of both false positive and false negative results.

Responsibility for spearheading HCP- and patient-targeted educational campaigns on DTC BBM tests lies with all relevant stakeholder groups, including pharmaceutical and diagnostic companies, medical societies, patient advocacy groups, and government entities. Multi-stakeholder engagement in these educational efforts is necessary to facilitate wider dissemination of information from reputable sources and appropriate handling of DTC BBM tests.

3.5 | Ethical considerations

3.5.1 | The right to know or not know

Patients have the right to decide whether to undergo BBM testing and whether they wish to know the outcome of the test results.[47] To ensure patients have a comprehensive understanding of BBM tests, including their limitations and the implications of positive results, multiple educational resources are needed. The BBM Workgroup recommends developing patient resources covering how a decision to use a BBM test is made, how to prepare for results, how to interpret the results (including the distinction between the results being suggestive rather than conclusive and the possibility and implications of false positive/false negative results), and what to expect in terms of follow-up. This includes addressing potential repercussions of a positive BBM test, such as impacts on employment, driver licensing, insurance, and social stigma.

While not all patients may wish to know their BBM test results, we anticipate a growing interest as the availability of robustly validated AD BBM tests increase. The BBM Workgroup urges that if, after an initial evaluation, BBMs are being considered, patients and clinicians communicate about whether to proceed. Developing effective patient education materials on AD BBM testing should involve all relevant stakeholders. Participation from diagnostic companies, HCPs, pharmaceutical companies, patient advocacy groups, and government agencies is necessary for the widespread dissemination of these resources that will play a critical role in the decision-making processes among individuals considering these tests. Moreover, the development of interactive and/or online assessment tools should be considered to evaluate patient understanding of BBM tests to help empower the patient, an effort that will ultimately save valuable time for the clinician.

3.5.2 | Confidentiality

Prior to undergoing a BBM test, patients should be aware of the confidentiality considerations related to such testing. For instance, despite regulations under the Health Insurance Portability and Accountability Act (HIPAA) that aim to restrict insurers in the United States from accessing this information, access is not always prohibited. Consequently, some patients may face coverage denials or premium increases if a positive BBM test result is incorporated into their medical records.[48] Therefore, new legislation is necessary to safeguard confidentiality.[49] The BBM Workgroup calls on HCPs to inform patients about the entities that may have access to BBM test results and how these results could be used.

Furthermore, with the 21st Century Cures Act, patients now have access to their medical records.[50] This underscores the importance of patients having a thorough understanding of BBM testing and its implications before undergoing the procedure, to prevent misinterpretation of BBM test results that patients may encounter in their medical records.[51] Moreover, the BBM Workgroup strongly recommends including a statement in the medical record emphasizing that BBM test results should be interpreted in the context of the entire clinical assessment.

3.6 | Conclusions

Clinical adoption of BBMs will be needed to meet the increasing demand for an AD diagnosis, driven by the availability of DMTs and the growing number of individuals with dementia. BBMs for AD hold promise for early detection of AD pathology and timely intervention, especially in light of the shortage of dementia specialists. To facilitate the adoption of BBMs, evidence-based guidelines and comprehensive training programs for HCPs will need to be developed, particularly in primary care settings where BBMs hold the greatest potential. Additionally, the creation of patient-focused educational resources will be necessary to empower patients with a thorough understanding of BBM tests, their constraints, and ethical considerations. Engagement from all relevant stakeholders is required to ensure credible guidance and educational efforts are widely accessible. Moreover, generating evidence from large community-based studies encompassing diverse populations will be essential to accurately interpret BBM test results across different demographic groups. Implementing these recommendations will help ensure the effective integration of BBMs into clinical practice, ultimately improving patient outcomes and health-care delivery.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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