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PERSPECTIVE

Paving the way for Alzheimer's disease blood-based biomarkers in primary care

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Abstract

Blood-based biomarkers (BBBMs) for Alzheimer's disease (AD) have the potential to revolutionize the detection and management of cognitive impairment. AD BBBMs are not currently recommended for use in primary care but may soon be as research demonstrates their clinical utility for differential diagnosis and patient management. To prepare for the incorporation of AD BBBMs into primary care, several practical challenges must be addressed. Here, we describe four immediate challenges: (1) preparing primary care providers to order and disclose AD BBBMs, (2) expanding the dementia-capable workforce, (3) ensuring equitable uptake of AD BBBM testing, and (4) securing access to AD treatment. We conclude by discussing future directions and challenges for use of AD BBBMs in primary care, including screening for preclinical AD and dementia detection algorithms.

KEYWORDS
Alzheimer's disease, biomarkers, dementia-capable care, primary care

Highlights

- Alzheimer's disease (AD) blood-based biomarkers (BBBMs) may be well suited for primary care.
- Many changes are needed to prepare the workforce and ensure patient access.
- Paving the way for AD BBBMs in primary care will require a multi-pronged approach.

1 | INTRODUCTION

The memory care system is under strain. Specialty memory clinics are presently understaffed due to a shortage of dementia specialists. Many prospective patients live far away from the nearest memory clinic, which can be a barrier to access. Wait times for those who do access specialty care can already extend to several months and are only expected to increase.[1] Further, US Food and Drug Administration (FDA) approval of disease-modifying therapies for Alzheimer's disease (AD), like lecanemab (Leqembi), are amplifying demand for and adding to the complexity of memory care.[2] Projected increases in the number of people living with mild cognitive impairment (MCI) and dementia threaten to further overwhelm the memory care system in the coming decades.

Of course, specialty clinics are not the only setting for memory care. A majority of primary care providers (PCPs) "believe they are on the front lines of providing critical elements of dementia care for their patients."[3] Indeed, one study found that the majority of dementia diagnoses in Medicare claims were first documented in primary care rather than in a specialty setting.[4] Moreover, many older adults would prefer

to receive care from community-based geriatricians or PCPs.[5] As the population continues to age and more disease-modifying therapies for AD become available, PCPs are expected to play an ever-greater role in early detection and diagnosis as well as treatment and management.[6] Yet, research has repeatedly shown that barriers exist to detecting cognitive impairment and diagnosing AD in primary care. These include low confidence in the diagnosis and lack of available tests that are feasible for use in primary care.[3,7]

Many experts have pointed to new blood-based biomarker (BBBM) tests for AD as a potential tool to address some of these barriers and thus aid PCPs with cognitive evaluations and diagnosis.[8–10] Blood-based tests are cheaper and less burdensome than other biomarker testing modalities such as positron emission tomography (PET) and cerebrospinal fluid (CSF), which are not readily accessible in primary care settings. Without the need for specialized facilities or procedural expertise, blood-based tests can be administered widely, but there may be other barriers to their adoption in primary care. Limited studies exist regarding PCPs' attitudes toward AD BBBMs. One qualitative study of 30 clinicians, 16 of whom were family or internal medicine practitioners, found mixed support.[11] Some practitioners felt BBBMs could improve access to AD diagnostics in primary care and increase PCPs' diagnostic confidence. By contrast, others expressed concerns about PCPs' current lack of knowledge about AD diagnosis and management, and several questioned the utility of making a diagnosis of AD or were concerned that learning BBBM results could have negative emotional effects on patients and families. Given this range of perspectives, it is unlikely AD BBBMs will be adopted in primary care settings without targeted efforts.

Calls to expand PCPs' involvement in memory care are happening at an auspicious, yet complicated, time. Several AD BBBMs are now available for clinical use, and others are in the development pipeline. Though their use in primary care is not currently supported,[12,13] that is likely to change in the near future. To smooth this adoption, critical areas of need must be addressed. Here, we identify four shorter term challenges and outline solutions for clinicians and other stakeholders to begin; we then highlight future developments likely to impact primary care should use of BBBMs become widespread. While these challenges may be relevant across the world, we focus on the US context and note that these challenges may vary based on the health-care system, demographics, and economic conditions of each country.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature. Currently published studies on the return of Alzheimer's disease (AD) biomarkers largely focus on amyloid positron emission tomography in research studies. There have not been published studies reporting the impact of returning AD blood-based biomarkers (BBBMs) on primary care patients.
2. **Interpretation**: To prepare for the incorporation of AD BBBMs into primary care, several practical challenges must be addressed. We describe four immediate challenges: (1) preparing primary care providers to order and disclose AD BBBMs, (2) expanding the dementia-capable workforce, (3) ensuring equitable uptake of AD BBBM testing, and (4) securing access to AD treatment.
3. **Future directions**: While AD BBBMs are not presently ready to be deployed within primary care, there is hope that they soon will be and that this will improve diagnostic processes. Accomplishing this will require adequate primary care provider training and ensuring a dementia-capable workforce is in place to offer collaborative care.

2 | TODAY'S NEEDS

For the promise of BBBMs to become reality, it is essential to prepare the primary care workforce, expand the larger dementia-capable workforce, and ensure health-care accessibility.

2.1 | Preparing PCPs for disclosure

To incorporate AD BBBMs into primary care, PCPs need training in the broader topics of diagnosis and management of AD and AD and related dementias (ADRD). Targeted clinician education can improve their knowledge, skills, and comfort facilitating an optimal cognitive evaluation and diagnostic work-up of patients presenting with cognitive complaints.[14] Training should include information on: the biological bases of AD/ADRD, the value of AD/ADRD diagnosis for informing treatment eligibility and psychosocial care, and the role of AD biomarker tests in diagnosis and management (including the need to continue an evaluation for other neurodegenerative causes of cognitive impairment in patients with negative AD biomarkers). Ideally, this training would also assist PCPs in identifying patients who are and are not appropriate for referral to specialty memory care. To deliver this training, state medical boards could include these topics in activities for maintenance of board certification, while specialist societies and private organizations can provide Continuing Medical Education credit for completion of relevant training.

At the same time, it will be important for research to continue advancing the evidence base for the clinical utility of AD BBBMs; appropriate use criteria and the development of best practices, including guidance on different available tests and appropriate situations for the use of AD BBBMs with one versus two cut points, will be needed. Professional societies and expert panels[15] can help disseminate knowledge of differences in test characteristics. At a health system level, clinical and operations leadership should closely examine performance of available AD BBBMs to select and promote the use of tests with optimal positive and negative predictive values for their clinical populations.

Resources developed through studies of AD biomarker disclosure already exist[16–18] and may help prepare clinicians who are ordering testing and seeking to disclose AD BBBM results. Disclosure of AD biomarkers in research settings has generally been formalized, but there are useful principles that can be adapted and applied to a primary care setting.[17–19] For instance, existing biomarker disclosure protocols emphasize the need for pre-test education, which includes providing individuals—and, as appropriate, their care partners—with information about the biological basis of AD, purpose of biomarker testing, possible results, the relevance of results for diagnosis, possible next steps for care, and limitations of biomarker tests (e.g., false positive/negative results, predictive utility of result). Pre-disclosure educational materials developed by the Advisory Group on Risk Evidence Education for Dementia[20] (AGREEDementia) may be shared with patients and their care partners. After testing, patient-friendly aids may facilitate disclosure of the result to the individual and care partner, promote understanding of the result, and provide a record of the result and key information for later review. Summaries of frequently asked questions and sample responses that have come up during the disclosure process have also been published[17] and may be useful for preparing PCPs to anticipate and answer patient and care partner questions during the disclosure process. After the result is disclosed, it is appropriate to follow up with the patient depending on their understanding of the result, psychological well-being, and needed next steps (e.g., treatment options).

Safety has been a primary concern in discussions regarding return of AD biomarker results to individuals across the cognitive spectrum, whether patients or research participants. Studies of apolipoprotein E and amyloid disclosure offer reassurance that this information can be returned without clinically significant psychological impact—that is, anxiety, depression, or suicidality.[19] However, limited data exist regarding the impact of returning of AD biomarker results to primary care patients. The documentation of a positive result in the medical record may have implications for insurability and stigmatization.[21]

2.2 | Expanding the dementia-capable workforce

Unfortunately, AD BBBMs are entering an environment characterized by health disparities. Racial and ethnic minorities experience higher incidence and prevalence of dementia and also face more barriers to accessing care,[22–24] which contributes to higher rates of missed and delayed diagnoses.[7] Disparities also exist for people living in rural areas[25] who have fewer care options and lower likelihood of living near specialized memory care clinics. If the introduction of AD BBBMs into primary care is to ameliorate rather than exacerbate disparities, there is a need to explicitly plan for the needs of these populations.

Expanding the dementia-capable workforce can help connect people with care, including but not limited to BBBMs. For example, having nurse practitioners within primary care settings may reduce health disparities for racial and ethnic minorities, particularly if the patient and provider are of the same race or ethnicity.[26] In rural areas, nurse practitioners play an important role in the provision of care. Granting nurse practitioners full practice authority—the ability to deliver care and prescribe medication without physician supervision or collaboration—is part of improving the availability of health-care services in underserved areas. This is a matter of state law and suggests the need for legislative change in states that have not granted full practice authority to nurse practitioners.[27]

Other health-care workers also play an important role in providing dementia care, particularly after a BBBM-informed diagnosis is made. For example, social workers can help with care management. Incorporation of social workers into a collaborative care model offers a cost-effective means of connecting people with community-based services and supports.[28] The Care Ecosystem offers a model of collaborative care.[29] Its multidisciplinary care team is centered around the patient–caregiver dyad, the members of which receive direct, telehealth-enabled support and resources from an unlicensed dementia-trained care team navigator. The care team navigator serves as the main point of contact, connecting dyads with clinicians with dementia expertise, including nurses, pharmacists, and social workers as needed, and ensuring a comprehensive care plan is shared with the patient's PCP. The Care Ecosystem is currently being tested in a pragmatic clinical trial across six health systems (R01 AG074710-01). Thus far, studies suggest this care model improves patient and caregiver outcomes and reduces health-care costs.[30]

A major barrier to providing this type of care is the difficulty of sustaining these programs, but there are mechanisms to support them. Introduced in 2018, the Centers for Medicare & Medicaid Services (CMS) Current Procedural Terminology code 99483 provides reimbursement to physicians, nurse practitioners, clinical nurse specialists, and physician assistants for comprehensive clinical visits that include "a multidimensional assessment that includes cognition, function, and safety; evaluation of neuropsychiatric and behavioral symptoms; review and reconciliation of medications; and assessment of the needs of the patient's caregiver" and result in a written care plan. Payment for comprehensive cognitive care exists, but it is difficult for PCPs to meet these requirements alone. Expansion of clinical teams would both increase access to comprehensive care and allow for payment for those services to sustain the programs.

2.3 | Ensuring equitable uptake of AD BBBM testing

First, continued research in collaboration with minoritized communities is of utmost importance to ensure biomarker results are valid for diverse populations; to date, validation studies have largely comprised White participants, and measurement thresholds may not be generalizable. Even when these tests are validated, it should not be assumed that there will be equal uptake of AD BBBM testing across the population. Unfortunately, there is inequitable uptake of numerous routine screening measures in primary care—such as mammography,[31] colorectal screening,[32] and cholesterol screening[33]—by race. Reasons for these differences are multifaceted[34] and include provider bias, stigma, medical mistrust, and patient perceptions about disease susceptibil-

ity and the benefits of testing. Thus, strategies to address inequities must be multifaceted. Interventions discussed in the cancer screening literature include educating providers, sending reminders for screening, improving community awareness, and offering culturally tailored educational materials. Similar interventions should be considered and studied in the dementia-care context.

The Medicare Annual Wellness Visit (AWV) for patients ≥ 65 includes cognitive screening and can serve as an initial flag for abnormal findings. This would trigger a follow-up visit for a more thorough cognitive exam and use of biomarker testing, including BBBMs. AWVs are generally underused and there are well-documented disparities in their use.[35] There have been efforts to increase usage[36] as AWVs can close gaps in preventive care and facilitate advance care planning.[37]

Second, it is important to ensure access to AD BBBM testing for rural populations. It may be possible to use remote sample collection and telehealth disclosure to accomplish this. Across the United States, there are thousands of locations for people to get blood draws, including Walgreens, CVS, LabCorp, and Quest Diagnostics. Alternative collection methods, such as dried blood spots, may soon be available[38] and contribute to testing accessibility. Adoption of telehealth has grown in recent years,[39] accelerated by the COVID-19 pandemic, though reimbursement, licensing, and credentialing across state lines remain challenges. Evidence suggests that AD biomarker results can be safely and effectively disclosed using telehealth methods.[40]

Third, not all AD BBBM tests are covered by health insurers. This is likely to change as the evidence supporting the accuracy and utility of these tests expands. A study of > 1500 individuals found that a blood test measuring the ratio of phosphorylated-tau217 to non-phosphorylated tau performed as well or better than FDA-approved CSF tests to identify people with brain amyloid (as confirmed by PET).[41] FDA clearance or approval of AD BBBM tests would strengthen the case for insurance coverage. It will also be important to establish the clinical utility of these tests. Though PET or CSF confirmation of amyloid is necessary for receiving anti-amyloid therapies, it is possible that blood tests could be incorporated into the therapy eligibility and management pipeline and reduce the number of PET and CSF studies needed. BBBMs may eventually be sufficient for confirmation of amyloid on their own if they perform similarly to PET and CSF AD biomarkers. These scenarios would increase the likelihood that insurance companies would cover the tests.

2.4 | Securing access to treatment

The utility of BBBMs is not limited to diagnosis: results will also inform treatment decisions. Some clinicians opt not to disclose a dementia diagnosis because they mistakenly believe there are few benefits to disclosure given limited treatment options. Yet, many individuals want to know, and a diagnosis is typically necessary to access treatment or support. Clinician education about AD BBBMs, discussed above, should also address how results might inform referrals to services and supports or treatments, including but not limited to anti-amyloid therapies, that can address patients' symptoms and improve quality of life.

Understandably, there is great interest in anti-amyloid therapies. The testing and monitoring required for anti-amyloid therapies is not presently feasible in primary care settings, which means there will still be an important role for specialty memory clinics. Yet, PCPs and specialists may provide complementary care. One study found that in primary care, AD BBBMs combined with a brief cognitive test (the Mini-Mental State Examination) could be used to triage patients for disease-modifying treatment (i.e., ensuring patients are early in the disease process and have screened positive for AD biomarkers). The authors estimate that wait times at specialty memory clinics could nearly be eliminated within 3 years,[9] if testing were routinely implemented in primary care. This would allow memory clinics to dedicate more resources to prescribing and administering anti-amyloid treatments. Collaborative relationships and workflows need to be developed.

Access to treatment is also an equity issue. As with current AD BBBM thresholds, the efficacy and safety of anti-amyloid therapies needs to be effectively studied in representative samples. Further, the estimated annual cost of the anti-amyloid drug lecanemab is $26,500, putting the drug out of reach for many. Though CMS announced they will cover lecanemab under Medicare Part B if the patient is enrolled in a CMS-approved registry, co-pays for treatment and monitoring will be a barrier to access for some individuals. Moreover, private insurance companies are not currently offering coverage for anti-amyloid therapies. Ensuring patients can access evidence-based, affordable care, if they want to, is essential to realizing the promise of AD BBBMs.

3 | TOMORROW'S ADVANCES

In Section 2, we outlined shorter term changes needed to facilitate adoption of AD BBBMs in primary care. Yet, the role of AD BBBMs will continue to evolve, suggesting the importance of a long-term perspective. Here, we highlight two future challenges—preclinical screening and machine learning diagnostic algorithms—and consider how to prepare to meet them.

3.1 | Screening for preclinical AD

AD biomarker testing is clinically appropriate for people with cognitive impairment. However, if ongoing secondary prevention studies are successful, older adults without cognitive impairment may undergo biomarker testing to determine the appropriateness of preventive therapy. From a public health perspective, early detection and secondary prevention are cornerstones of reducing the projected burden of AD. Use of AD BBBMs in primary care could offer an ideal means of population screening, as blood tests' lower cost and burden will allow for general use and serial testing. One day, AD biomarker screening may more closely resemble cholesterol screening, becoming a routine part of preventive care.

Pushing the window of detection and treatment earlier, into the preclinical phase of AD, will expand the number of individuals in need

of care and could place substantial burdens on providers. It is estimated that 30% of older adults have detectable brain amyloid; this means millions of people have AD biomarkers, though risk of developing cognitive impairment varies depending on the specific biomarker. The benefits of treatments will need to be weighed against the costs, as unnecessarily treating people who may never develop cognitive impairment will be expensive and resource intensive. Biomarker research promises to offer more tools to differentiate between people who will go on to develop cognitive impairment from those who will not, though the research remains ongoing. As this information is better understood, PCPs will need education to inform their practice and to ensure patients understand the meaning of results for prognosis and care. The growing patient population will require further expansion of the dementia-capable workforce, as described in Section 2.

If clinical screening for preclinical AD expands, it will be important to consider issues that will arise beyond the clinic, including stigma and discrimination.[21,42] Protections will be needed to ensure people who learn they have preclinical AD do not face discrimination when purchasing insurance or in the workplace. While the Genetic Information Nondiscrimination Act (GINA) provides protections from certain types of discrimination for people who learn genetic test results, these protections do not apply to biomarker results. Calls for a "Biomarker Information Nondiscrimination Act" provide an outline of anti-discrimination policies that are needed in this new era of disease detection to safeguard people who learn they have preclinical AD.[21,42]

3.2 | Dementia detection machine learning algorithms in primary care

Dementia diagnoses are frequently delayed or missed entirely,[7,24] with some estimates suggesting that roughly half of all people living with dementia have not received a formal diagnosis.[43,44] To aid detection, researchers have sought to develop algorithms that can identify individuals who may have undiagnosed cognitive impairment.[45] For instance, the electronic health record (EHR) Risk of Alzheimer's and Dementia Assessment Rule[46,47] (eRADAR) generates a risk score for undiagnosed dementia based on 31 EHR predictors related to demographics, diagnoses, vital signs, medications, and health-care use. After a patient is flagged, PCPs can opt to conduct targeted cognitive testing to confirm. Coupled with AD BBBMs, algorithms like eRADAR may help PCPs identify patients most likely to benefit from specialty memory care. If AD BBBMs are routinely used as a screening tool, the results may inform the development of new algorithms to provide a risk prediction for developing cognitive impairment due to AD over the next 5 years, for example.

Improving algorithms will require health systems to adequately capture data for the EHR and researchers to identify relevant predictors. Already, algorithm development is under way using various biomarker, demographic, and cognitive data to predict neurodegeneration and AD-specific biological changes.[48] As algorithms for AD detection are developed and deployed, it will be important to ensure they do not propagate existing health disparities.[49] This includes minimizing use of biased data sets for training, eliminating reliance on incorrect assumptions, and assessing the impact of algorithms on care and disease outcomes across racial and ethnic groups.[50]

4 | CONCLUSION

There is great enthusiasm for AD BBBMs. While they are not presently ready to be deployed within primary care, there is hope that they soon will be and that this will improve diagnostic processes, inform care and treatment, and also address inequities. Accomplishing this will, however, require that PCPs are adequately trained and prepared to discuss the results and that a dementia-capable workforce is in place and funded to offer collaborative care. Changes are also needed in medical education, health-care financing, licensure and practice authority laws, and anti-discrimination laws. Collective efforts by health systems, policy makers, and clinicians can drive many of these changes. Researchers also have a role, as validation of AD BBBMs in representative samples and evidence for their clinical utility will strengthen the case for their use and the argument for insurance coverage. Paving the way for the use of AD BBBMs in primary care will require a multipronged approach. Without intentional efforts to enact these changes, the growing demand for memory care will tighten the bottleneck for AD diagnostics and therapeutics, further limiting patient access.

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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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