Blood Biomarkers and Early Detection of Alzheimer's Disease and Related Dementias

Introduction

Alzheimer's disease and related dementias, or ADRD, represent a growing public health crisis, placing an increasing burden on patients, caregivers and the health system.[1] Alzheimer's disease accounts for 60% to 80% of dementia cases.[2] In the United States, it is estimated that more than one in five adults aged 65 and older have mild cognitive impairment, or MCI, and up to one in 10 have dementia.[3] However, over 90% of Medicare beneficiaries with MCI remain undiagnosed.[4] Patients with cognitive impairment often present late in the disease course, missing opportunities for early intervention.

Early identification of cognitive impairment can significantly improve patient care by enabling timely interventions, treatment and support. Historically, physicians have relied on clinical assessment, neuroimaging and analysis of cerebrospinal fluid, or CSF, to diagnose ADRD. However, recent advances in blood biomarkers (also referred to as BBMs or plasma biomarkers) present new opportunities for early detection, risk stratification and disease management, particularly in primary care settings.[5]

Primary care has a crucial role in transforming ADRD detection. While access to dementia specialists is limited, most Americans with ADRD receive routine care in primary care settings.[6] Thus, integrating BBM testing for AD-related pathology in primary care can provide an accessible pathway for early diagnosis and timely treatment.[7]

Health Disparities in Alzheimer's Disease and Related Dementias

Significant disparities exist in the prevalence, diagnosis and treatment of ADRD. For example, researchers have noted that Black women in the United States are at increased risk for the development of ADRD due to "a greater prevalence of vascular risk factors such as hypertension and type 2 diabetes, coupled with unique social and environmental pressures."[8] In addition, Hispanic patients experience an average delay of 12 months in ADRD diagnosis compared with non-Hispanic white patients.[9] The underrepresentation of people from racial and ethnic minority groups across the spectrum of clinical trials for ADRD further complicates efforts to address disparities in diagnosis and treatment.[10]

Since primary care practices often reflect the diversity of their communities, primary care clinicians have an opportunity to bridge these gaps by improving early detection, diagnosis and treatment access. They also play a critical role in recruiting diverse populations into ADRD clinical trials, enhancing the generalizability of research findings.[10,11]

Case Finding and Early Detection of MCI and Mild Dementia

Primary care clinicians should be alert for early signs of cognitive impairment in older adult patients and incorporate cognitive assessments into routine care, such as the Medicare Annual Wellness Visit.[11,12] In addition, some patients with preclinical cognitive impairment may report subjective cognitive symptoms before detectable abnormalities appear on cognitive assessments.[13] A diagnosis of cognitive impairment should be considered when an office-based cognitive assessment is abnormal and/or when a patient or caregiver expresses concerns about cognitive function or memory loss.

Dementia is characterized by both cognitive and functional impairment, while MCI involves impairment in only one cognitive domain without significant functional impairment. Clinical judgment alone has been shown to be insufficient in reliably diagnosing MCI and dementia, with sensitivity and specificity in primary care as low as 34% and 58%, respectively.[14] Because MCI does not involve functional impairment, detecting the more subtle changes it causes may be even more challenging without a systematic evaluation.

Studies have shown that a systematic approach to evaluating cognitive concerns or abnormal cognitive results can be effectively integrated into primary care workflows.[12] This comprehensive medical evaluation should include the following:

- Use of validated cognitive screening instruments to confirm impairment
- Laboratory and imaging assessments to rule out addressable causes of cognitive decline

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- Medication reconciliation to identify potential cognitive side effects
- Comprehensive clinical assessment to determine the most likely underlying cause of cognitive impairment
- Counseling on lifestyle modifications to support brain health

Diagnosing MCI and dementia is crucial for identifying patients eligible for disease-modifying therapies, or DMTs, and for enrolling them in supportive care models such as Guiding an Improved Dementia Experience (GUIDE). When AD is suspected, BBM testing can serve as an adjunct to the diagnostic evaluation.[7] Shared decision-making is essential to ensure patients and caregivers understand the benefits, limitations and implications of BBM testing.

The Role of Blood Biomarkers for Alzheimer's Disease

Amyloid positron emission tomography, or PET, and CSF biomarkers have long been validated and used in AD diagnosis due to their high accuracy.[5] However, their limited scalability and accessibility make them impractical for widespread early detection. BBM testing has emerged as a viable alternative, detecting AD pathophysiological hallmarks such as amyloid-beta deposition, tau pathology and neurodegeneration.[15] Biomarkers of AD-related pathology can augment a clinical diagnostic evaluation to help stratify patients and differentiate the likelihood of AD from the likelihood of other dementia syndromes that can have overlapping clinical presentations.

Key BBMs with potential diagnostic utility include:

- **Plasma amyloid-beta (Aß42/Aß40 ratio):** This BBM predicts amyloid plaque burden in the brain.[16,17]
- **Phosphorylated tau (p-tau181, p-tau217):** Counterintuitively, this BBM is most strongly associated with amyloid pathology, in addition to having some correlation with tau pathologies.[18-20] It may be more predictive of incipient memory loss in presymptomatic patients, but this is unproven, so p-tau is not used in that context yet.
- **Neurofilament light chain:** NfL is a marker of neuronal injury that differentiates AD from non-neurodegenerative conditions.[21,22]

Among these BBMs, p-tau217 has demonstrated the highest accuracy in predicting amyloid PET positivity.[23,24] Combinations of biomarkers, particularly with p-tau217, may further improve diagnostic precision, but additional research is needed.[25]

Clinically available BBMs for AD are expected to evolve as new biomarkers are identified.[26] Unlike amyloid PET, BBM performance varies across laboratories and platforms, complicating implementation.[5] Until these tests are standardized, it is important for primary care clinicians to understand the performance characteristics of the assays available to them. To support this, the Global CEO Initiative on Alzheimer's Disease recently launched a Blood Test Performance Database (www.alzbiomarkerhub.org/performance-database-tool) to guide clinical decision-making.

Benefits of Blood Biomarker Testing in Primary Care

Key advantages of BBM testing in primary care include the following:

- It is noninvasive and easier to administer than CSF analysis.[27]
- It is scalable, accessible and likely to be cost-effective.[7,15]
- By integrating it into routine care, primary care clinicians can identify high-risk patients earlier and initiate timely interventions.[5,28]
- It provides information that can improve patient and caregiver planning, as well as enable patients to make early lifestyle modifications and explore potential participation in clinical trials.[29]

Blood Biomarker Testing in Primary Care

Primary care clinicians may find BBM testing for AD most useful for patients who:

- Exhibit cognitive impairment with objective deficits on cognitive assessments, even if their impairment does not interfere with independence in daily activities[30]
- Have mild dementia and may be candidates for DMTs
- Have cognitive impairment or dementia with an unclear underlying diagnosis that requires further clarification

Until additional research on BBMs in primary care populations is available, BBM testing should be viewed as a tool to evaluate the level of concern for AD, not a confirmatory diagnostic test.[7,24] When addressable causes of a patient's cognitive impairment have been ruled out, BBM testing can play a role in the clinical identification of patients who are less likely to have amyloid pathology. This reduces the need for some patients to wait for access to a dementia specialist for diagnosis or treatment discussions.

Experts do not recommend BBM testing for patients without any cognitive impairment because it may confuse the clinical diagnosis.[7] Blood biomarker tests may be inaccurate in cognitively normal or asymptomatic patients and lead to unnecessary psychological distress. At this time, there are no approved treatments for patients without cognitive impairment, and the use of BBMs to predict future risk is not recommended. For cognitively normal

patients who have concerns or complaints about cognitive function or memory loss, referral for more detailed neuropsychological testing may be useful.

CONSIDERATIONS FOR BLOOD BIOMARKER TESTING IN PRIMARY CARE

While BBMs are helpful in clinical practice, challenges associated with BBM testing in primary care include the following:

- **Training and interpretation:** Primary care clinicians must be equipped to interpret results and counsel patients appropriately.[5]
- **Variability:** BBM test accuracy varies across different laboratories and commercial testing platforms.[27] In addition, some chronic conditions (e.g., chronic kidney disease, obesity, cardiovascular disease) have been shown to impact the level of BBMs but not CSF or PET biomarkers.[24] Certain medications may also impact BBMs.[24]
- **Insurance coverage:** Most health insurance plans do not currently cover BBM testing, leaving patients responsible for the cost.[31]

The following are also considerations for BBM testing in primary care:

- The U.S. Food and Drug Administration's regulatory framework for laboratory developed tests, including BBM tests, is evolving.[32]
- For approximately 14% of BBM test results, biomarker assays report as "indeterminate" or are uninterpretable.[33] Explaining these results to patients and discussing next steps is difficult and may lead to additional testing.
- Referral and treatment pathways for AD may not be available or accessible.

BLOOD BIOMARKER TESTING AND TREATMENT PATHWAYS

BBM testing can assist in stratifying patients for appropriate diagnostic and treatment pathways.[7] If a BBM test is negative but clinical suspicion for AD remains high, repeat testing in six to 12 months may be considered. In addition, BBMs help identify candidates for disease-modifying therapies. As of 2023, 79% of AD drugs in clinical trials were DMTs.[34] Currently available DMTs are most effective at earlier stages of cognitive impairment. They have been shown to promote clearance of amyloid-beta deposits in the brain by as much as 55% to 85%,[35] although questions remain about whether they achieve longer-term meaningful changes in cognitive and clinical function.[12]

Some patients receiving DMTs develop vasogenic or hemorrhagic changes detected on magnetic resonance imaging that are called amyloid-related imaging abnormalities, or ARIA.[36] This condition is more common in patients with a higher amyloid burden, a history of thrombotic or hemorrhagic stroke(s), or multiple apolipoprotein E 4 alleles, as well as in patients who are on anticoagulants. Therefore, identifying patients who are eligible for DMTs requires early detection and careful review of exclusion criteria. As research on DMTs advances, it may be helpful for primary care clinicians to incorporate discussion of these therapies into shared decision-making with patients with early cognitive impairment and positive BBM test results who may be candidates for DMTs.[37]

Future Directions

As BBM testing becomes more widely available, primary care clinicians will play a crucial role in the early detection and management of ADRD. Steps to enhance the integration of this tool into practice include the following:

- Ongoing education and training on BBM testing and dementia care pathways
- Multidisciplinary collaboration with neurologists, geriatricians, pharmacists and social workers
- Patient-centered communication strategies to navigate discussions about dementia risk and diagnostic uncertainty

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