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Alzheimer Disease Biomarkers in Clinical Practice: A Blood-Based Diagnostic Revolution

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Abstract

An estimated 6.1 million Americans live with cognitive impairment—a number that is expected to triple by 2050. Alzheimer disease (AD) is the most common cause of impairment. The development of blood-based biomarkers capable of detecting pathological changes of AD in living patients has the potential to revolutionize the diagnostic approach to cognitive impairment by enabling screening for AD using accessible, non-invasive measures of amyloid and tau neuropathology, with accuracy that increasingly approaches that seen with "gold standard" positron emission tomography and cerebrospinal fluid measures. Demand for biomarker testing is expected to intensify with the emergence of effective treatments for AD and related dementias. Clinicians in all fields must prepare to meet this demand. Primary care practitioners are well positioned to support dementia diagnosis and management, including the application and interpretation of biomarkers. This article reviews the current uses of AD biomarkers and the potential applications of emerging blood-based AD biomarkers in clinical practice.

Keywords

Alzheimer disease, blood biomarkers, amyloid, tau, dementia, mild cognitive impairment, screening

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Introduction

An estimated 6.1 million Americans are living with cognitive impairment.[1] These numbers are expected to triple by 2050,[2] increasing demand on an already strained clinical workforce. Alzheimer disease (AD) accounts for the majority of cases of dementia. Historically, the diagnosis of symptomatic AD has relied upon detection of a characteristic profile of neurocognitive deficits that typically include prominent progressive short-term memory loss, with confirmation established through detection of cerebral amyloid plaques and tau tangles at death.[3] This approach runs counter to patients' and caregivers' desire for timely diagnoses,[4] and exemplifies the need for biological markers that can be reliably and safely measured, and used to advance the diagnosis and treatment of patients with symptomatic AD.

A biomarker is an "indicator of normal biological or pathologic processes, or responses to an exposure or intervention, including therapeutic interventions."[5] Biomarkers are not new in clinical practice. Practitioners routinely use biomarkers to diagnose and monitor patients with diabetes (serum hemoglobin A1C), hyperlipidemia (serum high-density lipoprotein/low-density lipoprotein, triglycerides, and cholesterol), prostate cancer (serum prostate-specific antigen), ovarian cancer (serum cancer antigen 125), and acute coronary syndromes (serum troponin). Neither are biomarkers new in AD. Neuroimaging- and cerebrospinal fluid-based biomarkers of amyloid and tau neuropathology have been used to quantify brain changes associated with AD in research participants for years.[6,7] The extension of research biomarkers to clinical practice has the potential to improve the diagnostic evaluation of patients with cognitive impairment, allowing patients with symptomatic AD to be diagnosed earlier and with greater confidence.[8] Furthermore, the emergence of less-invasive blood-based biomarkers may further expand the application of this technology, enabling screening to take place in primary care clinics, revolutionizing the diagnostic approach to cognitive impairment.

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Primary care practitioners are well positioned to meet the rising demand for practitioners with expertise in dementia diagnosis and care. Recognizing this, we summarize the current uses of AD biomarkers in clinical practice and review the literature concerning emergent blood-based AD biomarkers. Special focus is paid to discussion of implications of emergent blood-based AD biomarkers in the primary care setting.

Studies included within this commentary were identified through a targeted search of the MEDLINE (1946-2022) database, including English-language studies in humans. There were no limits to publication date. The search strategies were created using a combination of keywords and standardized index terms, including MeSH, Embase/Emtree terms, and keywords such as Alzheimer disease, Alzheimer dementia, blood-based biomarkers, amyloid beta, $A\beta_{42}$/$A\beta_{40}$, phosphorylated-tau, p-tau, p-tau_{181}, and p-tau_{217}.

Addressing the Need

Primary care practitioners bear the brunt of the burden of assessment of patients with new memory complaints. Yet worryingly, a survey commissioned by the Alzheimer's Association revealed that half of primary care practitioners believed that the medical profession was "not prepared for the expected increase in demand" for dementia care. The majority also expressed concern that there were not enough specialists to manage patient referrals.[9] Limitations in training contribute to the dearth of appropriately trained practitioners. A survey of post-graduate medical trainees (residents) in the United States confirmed that post-graduate trainees received, on average, 8 h of formal training on AD and related dementias over the course of their primary care residency programs. As a result, 72% reported feeling "somewhat," "not very" or "not at all prepared" to diagnose and manage patients with cognitive impairment.[9] Compounding issues with training, primary care practitioners are stretched for time due to increasingly shortened office visits, which are consumed by increasingly complex patients. Collectively, these factors contribute to under-recognition and misdiagnoses of cognitive impairment in clinical practice (Figure 1). These challenges highlight a need that could be addressed by expanding training for primary care practitioners concerning the assessment, diagnosis, and management of patients with dementia—a task that will be advanced by specialized knowledge concerning the appropriate use of disease-specific biomarkers in clinical practice.

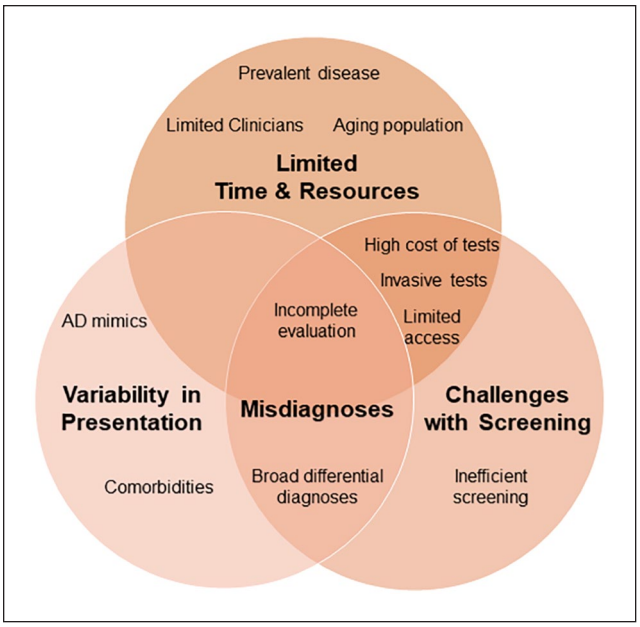

Figure 1. Diagnostic challenges in Alzheimer disease. The accurate diagnosis of Alzheimer disease requires a detailed history, physical examination and testing to rule-in Alzheimer disease and rule-out other causes of cognitive impairment. The initial workup for cognitive complaints typically includes a standardized mental status assessment (Montreal Cognitive Assessment, Mini-Mental Status Examination), screening for B12 deficiency and thyroid dysfunction, and often neuroimaging (brain magnetic resonance imaging or computerized tomography). Limited time and resources, variability in the clinical presentation and inefficacies in screening challenge accurate and efficient recognition of cognitive impairment in clinical practice and contribute to underdiagnoses and misdiagnoses of symptomatic Alzheimer disease.

AD Biomarkers in Clinical Practice

The optimal evaluation of patients with cognitive impairment necessitates that a detailed history be obtained from the patient and a reliable collateral source (eg, spouse, adult child, other family member, or friend), and integrated together with examination findings and bedside tests of cognition.[3] Routine blood tests and neuroimaging should be leveraged, when appropriate, to exclude other causes of impairment.[3] Primary care practitioners already possess these skills, and routinely accomplish these tasks amidst a busy schedule, seeking specialist opinions when necessary.

The development of biomarkers of amyloid and tau has made it possible to reliably measure AD neuropathology during life, taking the standard clinical assessment to the next level. Longitudinal studies establish a relationship between changes in markers of cerebral amyloid and tau neuropathology, and the timing and severity of cognitive symptoms, and findings at brain autopsy.[10-12] Decreases in cerebrospinal fluid levels of amyloid are one of the earliest measurable findings in patients with AD, with changes paralleling the formation and accumulation of amyloid plaques within the brain (measured by amyloid positron emission tomography [PET]).[7,13] The accumulation of cerebral amyloid in persons without cognitive complaints defines the preclinical or presymptomatic phase of AD, which typically

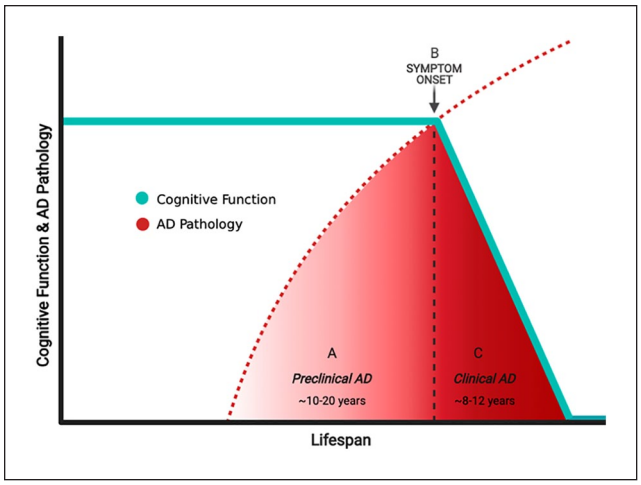

Figure 2. The relationship between Alzheimer disease (AD) pathology and cognitive function across the lifespan. Accrual of AD neuropathology begins decades before the emergence of cognitive complaints, identified as the "preclinical" (or presymptomatic) period (A). Declines in cognitive function attributable to AD neuropathology herald the onset of "clinical" (or symptomatic) AD (B), a period that commonly lasts between 8 and 12 years (C). The protracted "preclinical" period presents an ideal time during which treatments could be provided to at-risk individuals to prevent or reverse the accrual of AD neuropathology and delay the onset or progression of clinical AD.

spans 10 to 20 years (Figure 2).[14] Symptoms of cognitive impairment emerge in lockstep with the accumulation of tau neuropathology (measured via tau-PET imaging or cerebrospinal fluid measures of total- and phopsphorylated$_{181}$-tau) and neuronal degeneration—events that mark the onset of the shorter "clinical" or symptomatic stage of AD.[10] The clinical stage of AD may be mild at first ("mild cognitive impairment"), with progression to dementia and death occurring over a variable period often lasting 8 to 12 years. These findings suggest that AD neuropathology accumulates gradually over time, leading to neuronal failure, degeneration, and ultimately cognitive impairment, and death.[15]

Although AD biomarkers have mainly been applied in the research setting, clinical applications are becoming clearer. In a US-wide study of patients with mild cognitive impairment or atypical dementia, access to amyloid-PET imaging improved diagnostic confidence, and influenced clinical management in the majority of patients.[8] Patients and caregivers also indicate that they want access to AD biomarkers—particularly when biomarker results may improve access to resources.[4,16] The demand for biomarkers is likely to increase even more with the rising prospect of disease-modifying therapies for AD[17-21] and expansion of clinical trials evaluating investigational agents designed to prevent cognitive impairment in patients at high risk of developing dementia due to AD.[22,23]

Established AD biomarkers include PET-neuroimaging and cerebrospinal fluid measures. However, PET-based measures are costly, are seldom covered by insurers, and require access to specialized neuroimaging infrastructure and expertise.[24] These limitations render them inaccessible to most people. Although cerebrospinal fluid biomarkers are more accessible—with commercial laboratories across the United States providing quantitative measures of amyloid, total tau, and phosphorylated tau[25-27]—diagnostic lumbar punctures are perceived as invasive, and require skilled operators to perform.[28] As a result, these biomarker measures are unlikely to be widely applied outside of academic and subspecialty settings, presenting obvious challenges to wide dissemination and application in clinical practice. The emergence of blood-based measures of amyloid and tau pathology promises to change this.

A Blood-Based Revolution

Blood-Based Measures of Cerebral Amyloid

The advent of immunoprecipitation mass spectrometry assays capable of measuring minute amounts of isoforms in blood accelerated the development of blood-based measures of cerebral amyloid. Aβ_{40} is the most common variant of amyloid found in the brain, and plasma levels are relatively consistent across populations. Aβ_{42}, on the other hand, is more prone to aggregation and predominates in amyloid plaques that define AD.[29] Ratios of these isoforms (Aβ_{42}/Aβ_{40}) in cerebrospinal fluid are highly specific for the presence of AD neuropathology, with decreases in the ratio associated with increases in cerebral amyloid plaque deposition.[7,30,31] Only recently were these findings replicated in blood-based measures.

In 2017, a group at Washington University in St. Louis (Saint Louis, MO) successfully demonstrated that decreases in plasma Aβ_{42}/Aβ_{40} differentiated amyloid "positive" versus "negative" individuals, determined using "gold standard" cerebrospinal fluid and amyloid-PET biomarkers.[32] Furthermore, participants who had a negative amyloid-PET at baseline but abnormal plasma Aβ_{42}/Aβ_{40} measures had a 15-fold greater risk of converting to amyloid-PET "positive" status across follow-up than patients with normal plasma amyloid levels.[33] These findings suggest that plasma biomarkers may represent an earlier measure of cerebral amyloid status in preclinical patients.

These findings have been reproduced in additional studies engaging hundreds of participants with and without cognitive impairment, which cumulatively affirm the ability of blood-based measures of amyloid to reliably discriminate between individuals with and without clinically significant cerebral amyloidosis with excellent sensitivity and specificity (receiver operating characteristics demonstrate an area under the curve of 0.85-0.97).[32-37] These advances

culminated in FDA-approval of a blood test that quantifies plasma $A\beta_{42}/A\beta_{40}$ levels (approved for clinical use in the US; October 2020). Its suggested use is for symptomatic individuals only, with testing limited to a select commercial providers.[38,39] Studies defining the utility of this test in broad populations of patients are needed to inform the generalizability of research findings and practical limitations.

Blood-Based Measures of Tau Neuropathology

Since 2018, studies have shown that blood-based measures of phosphorylated-tau (p-tau) correlate with cerebrospinal fluid and PET measures of amyloid and tau neuropathology, and with symptomatic disease progression.[40-48] From a diagnostic perspective, measures of $p\text{-}tau_{217}$ isomers appear to hold the greatest promise. Independent studies support its sensitivity and specificity for AD,[40,42,43,45] while a head-to-head study established superiority of $p\text{-}tau_{217}$ measured by mass spectrometry for the diagnosis of symptomatic AD over 9 other immunoassays, with near-perfect ability to discriminate participants with AD (area under the curve of 0.95).[48] Commercial blood-based markers of tau neuropathology are not yet available but are expected in the near future.

Increases in plasma $p\text{-}tau_{217}$ levels may precede changes in tau-PET, and even amyloid-PET.[42,43,46] Thus, elevations in plasma $p\text{-}tau_{217}$ may mark the earliest stages of "preclinical" or "asymptomatic" AD. Although the ability to identify asymptomatic patients at-risk of developing cognitive impairment offers little-to-no clinical benefit at the present time, the prospect of effective disease-modifying therapies for AD justifies continued research in this area.

Clinical Applications of Blood-Based Biomarkers

Expanded access to blood-based biomarkers of amyloid plaques and tau tangles promise to revolutionize dementia diagnosis and care, facilitating surveillance and early detection of AD in susceptible individuals and increasing the demand for biomarker testing in symptomatic individuals. Clinicians in all fields must prepare to meet this demand. This will require appropriate training in the proper use of these tests and interpretation of results, in addition to the development of standardized protocols and frameworks to guide AD biomarker testing in practice. The appropriate use guidelines developed for clinical research provide an excellent starting point for clinical guidelines.[49]

While patients (and providers) often focus on the potential benefits of testing, there are practical downsides that warrant consideration.[50,51] Knowledge of one's amyloid or tau status, and therefore likely risk of AD, may influence access to healthcare and insurability (specifically, long-term care, disability, and life insurance), as well as decisions concerning employment, driving, and independent living. Findings in one patient may also have implications for other family members (eg, future risk of AD, insurability, etc.).[52] Informed decisions concerning AD biomarker testing will necessitate a clear discussion and documentation of reasons for biomarker testing (ie, perceived benefits), potential risks, and alternatives. As in other areas of controversial testing (eg, genetic testing), adequate resources should be offered to patients who elect to undergo testing, and health care providers must be equipped and prepared to deliver these resources.

Future Directions

The ability to objectively measure disease-specific brain changes through a simple blood draw represents a milestone in AD diagnosis and evaluation. Beyond implications for clinical care, the validation of blood-based biomarkers of AD will allow widespread screening of cognitively normal community-dwelling individuals, with the potential to identify individuals at the highest risk of developing symptomatic AD who may benefit from participation in clinical trials of putative AD-modifying therapies designed to prevent the onset of cognitive impairment.[24] The possibility that serial blood-based measures may reflect cerebral amyloid and tau pathology also raises the potential that biomarkers may serve as interim markers of drug efficacy, accelerating discovery and evaluation of medications designed to slow, arrest, or clear amyloid plaques and tau tangles.[19] Access to efficacious therapies for AD will prompt substantial investment in AD research. This investment will, in turn, support further diagnostic and therapeutic advances, catalyzing the discovery and validation of better biomarkers and biomarker panels, and further increasing patient and caregiver interest and demand for testing.[53] Already work is underway to refine techniques capable of measuring nano-sized membrane-bound extracellular vesicles that are released by all living cells and used to shuttle molecular cargo across the blood-brain barrier. Early work with nanoparticle tracking analysis and cryo-electron microscopy suggests that it may be possible to measure vesicles contents, including proteins, mRNA, lipids, and other nucleic acids.[54] Although speculative, progress in this area may further inform the diagnosis, staging, and monitoring of neurodegenerative diseases, representing another substantial step toward a blood-based diagnostic revolution.[54,55]

Conclusions

Rising demand coupled with the declining capacity of dementia specialists threatens to further widen the gap in dementia care. Primary care practitioners with experience in dementia diagnosis and care have a vital role to play in addressing patients' questions, concerns, and requests for non-invasive testing, and supporting interpretation of test results on a patient-by-patient basis. Providers with this

requisite expertise are needed to stand in the gap while training programs are developed, implemented, and scaled to meet demand.

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GS Day serves as a topic editor on dementia for DynaMed Plus (EBSCO Industries, Inc), consultant for Parabon Nanolabs Inc, and as clinical director for the Anti-NMDA Receptor Encephalitis Foundation. He holds stock in ANI Pharmaceuticals Inc and has provided record review and expert medical testimony on legal cases pertaining to management of Wernicke encephalopathy.

Author Contributions

M Paczysnki participated in study design; acquisition and interpretation of data; drafting and revision of the manuscript. GS Day participated in study design; acquisition and interpretation of data; revision and finalization of the manuscript.

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