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SPECIAL ARTICLE

Rational Use of Blood-Based Biomarkers for Alzheimer's Disease: Navigating Between the Hope and the Hype

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ABSTRACT

With better understanding of the pathologic processes of Alzheimer's disease, diagnostic methods have been developed to focus on specific biomarkers of disease detectable on brain imaging, cerebral spinal fluid, and, more recently, plasma. Although these tests do not establish a diagnosis of dementia, which requires a clinical evaluation, they can more precisely identify whether Alzheimer's disease is a contributing cause. The recent FDA approval of two blood-based biomarkers and the availability of others, including direct-to-consumer tests, has led to the potential for widespread use in primary and specialty care. However, the currently available blood-based biomarkers are more highly correlated with amyloid brain PET scans, which are less specific for symptomatic Alzheimer's disease, than with p-tau brain PET scans, which are strongly associated with changes in cognition. The value of a positive or negative blood-based biomarker depends on the test characteristics (e.g., sensitivity and specificity) of the specific test as well as the prevalence of the disease in the population. Clinicians ordering blood-based biomarkers must decide their value in the care of individual patients and be prepared to interpret the test results to their patients.

1 | Introduction

These are remarkable times for Alzheimer's disease. As a result of substantial investment in research stimulated by the National Alzheimer's Project Act [1] and funded through the National Institutes of Health, industry, and philanthropy, major diagnostic and therapeutic advances have been made. Alzheimer's disease is now defined as a biologic process, regardless of whether clinical symptoms of dementia are present [2]. The prevailing understanding of the process includes three sequential steps: the extracellular accumulation of amyloid precursor protein Aβ42 fragments as plaques, the intracellular deposit of tau neurofibrillary tangles, and finally, the destruction of neurons [3]. Although the most common type of dementia is mixed, the vast majority of persons affected have an Alzheimer's disease component [4]. Drugs aimed at interrupting this pathogenic process of Alzheimer's disease have been approved by the Food and Drug Administration (FDA), though definitions of clinical benefit vary. An additional 138 drugs are in the pipeline [5].

Concurrently, there have been advances in diagnosing Alzheimer's disease, including brain imaging, cerebrospinal fluid (CSF) biomarkers, and, more recently, blood-based biomarkers. More accurate brain scans addressing underlying pathologies have been developed, particularly those that use p-tau tracers. A positive tau positron emission tomography (PET) scan establishes the diagnosis of Alzheimer's disease [6] but tau scans are less available for clinical practice; nor are they covered by Medicare. Amyloid scans, which are more widely available and have Medicare coverage, are less specific for symptomatic Alzheimer's disease and 25%–30% of persons with positive scans are cognitively unimpaired [7]. Moreover, among those who are cognitively unimpaired and have positive amyloid scans but negative tau scans, only approximately 20% will develop

Summary

- Key Points
  - Establishing a diagnosis of Alzheimer's disease is often a lengthy, imprecise process.
  - With the development of brain imaging of the underlying pathologic process, cerebrospinal fluid biomarkers, and, more recently, blood-based biomarkers, earlier and more accurate diagnoses are possible.
  - The strengths and limitations of currently available blood-based biomarkers must be considered in their appropriate use in geriatrics and primary care settings.
- Why does this paper matter?
  - With the development of new blood-based markers to diagnose Alzheimer's disease, clinicians who care for older patients will need to decide whether and when to order these tests. Recognition of the strengths, limitations, and implications of test results can help clinicians appropriately use these tests.

mild cognitive impairment (MCI) or dementia over the next 6 years [8].

Although CSF biomarker tests have been available and can predict the development of cognitive decline long before clinical symptoms appear [9, 10], because of the invasiveness of the lumbar puncture needed, these have not been used widely.

In light of the expense and logistic barriers in using imaging and CSF diagnostic approaches, there has been major interest in accurately diagnosing Alzheimer's disease using blood-based biomarkers. Similar to CSF biomarkers, these begin to change in midlife, long before clinical symptoms occur [11]. As of this writing, there are at least 16 commercially available blood tests for Alzheimer's disease (Table 1) [12, 13, 17]. Two are FDA-approved and one is obtainable direct-to-consumer. The available tests measure individual or combinations of biomarkers $pTau_{181}$, $pTau_{217}$, np-Tau_{217} ratio, Aβ42/Aβ40 ratio, and ß-Amyloid 1–42 plasma ratio. Some are reported as positive, negative, or intermediate based on cut-points; intermediate results require additional testing. Some approaches also include nonspecific markers of neuron damage (Neurofilament light chain, Glial Fibrillary Acid Protein) to better predict amyloid scan positivity. Regardless of their names, all currently available assays are correlated with brain amyloid status based on amyloid PET scans rather than tau PET scans [18, 19]. Hence, positivity on these markers is consistent with neuropathologic changes of Alzheimer's disease but a patient may still be cognitively unimpaired. Because of competing morbidity and variable rates of disease progression, some older patients may never develop symptoms during their lifetimes.

In clinical care, three considerations for ordering blood-based biomarkers are important: the setting where care is provided, test-specific characteristics (e.g., sensitivity and specificity), and whether the person being tested is symptomatic. In specialty settings (e.g., memory clinics), blood-based biomarkers may be valuable in the diagnostic process (if at least 90% sensitivity and 75% specificity for a reference test) or as confirmatory (at least 90% sensitivity and 90% specificity for a reference test) [20]. Nevertheless, blood-based biomarkers are also known to have analytical stability limitations [21] and testing samples outside of the manufacturer or laboratory-developed criteria may lead to inaccurate results.

Although caution has been expressed about the use of blood-based biomarkers in primary care [22, 23], their use in clinical practice is increasing and a 2024 Alzheimer's Association survey found that 91% of respondents would undergo a simple test (e.g., blood-based biomarker) before symptoms appear [24]. Hence, there has been interest in screening and public demand for testing among the "worried well". Physicians also may be driving demand because ordering blood-based biomarkers is a tangible action in a disease that has had so few actions available.

Recently, the FDA has approved Elecsys pTau181 for use in primary care based on the principle that the high negative predictive value (96.2%) [25] in excluding Alzheimer's disease would enable primary care providers to confidently tell patients that Alzheimer's disease is not the cause of their symptoms. Nevertheless, blood-based biomarkers are often falsely positive, especially when the prevalence in the population is low (e.g., middle-aged children of persons with Alzheimer's disease), leaving the ordering provider to explain what this means, including the likelihood that they will not develop symptomatic dementia during their lifetimes [26]. Such conversations are difficult, particularly for primary care providers who are often pressed for time and may have limited expertise in dementia care. Positive results in cognitively unimpaired persons may prompt additional testing and cause worry about whether and when they will convert to symptomatic Alzheimer's disease. Patients with positive results also run the risk of overtreatment with anti-amyloid drugs in the absence of symptoms, which no evidence, to date, would support.

Among symptomatic persons evaluated in primary care and specialty clinics, blood-based biomarkers have high diagnostic accuracy [27, 28]. If positive, these tests may also help facilitate access to specialists, including geriatricians, who can conduct appropriate diagnostic evaluation and may decrease disparities in timeliness of diagnosis in underrepresented groups, who often have barriers and delays in obtaining appropriate evaluation or seeing a specialist [29].

In contrast, these tests are currently not recommended for asymptomatic persons [30], although biologic staging (1 and 2) [31] of cognitively unimpaired persons who have positive biomarkers is an area of active research interest, including ongoing clinical trials [32, 33].

A rational current approach to blood-based biomarker testing would be to use them as diagnostic or confirmatory tests in persons who have objective cognitive impairment by clinical evaluation to confirm that Alzheimer's disease is at least part of the cause of their impairment. This is particularly important

TABLE 1 | Commercially available blood-based markers for AD from major US reference laboratories and validation against abnormal amyloid-PET scan (January 2026).

Biomarker	Performing laboratory/ test name	Test characteristics[a,b]	
		Sensitivity (%)	Specificity (%)
• Aβ42/Aβ40 ratio	Quest AD-Detect, Beta-Amyloid 42/40 Ratio[d]	93[b], 91[c] [12]	74[b], 91[c] [12]
• Aβ42/Aβ40 ratio • ApoE genotype • Age	PrecivityAD	92[c] [12]	77%[c] [12]
• pTau217	LucentAD p-tau	90[c] [12]	91[c] [12]
• pTau217	Quest	87[b], 92[c] [12]	72, 92[c] [12]
• pTau217	ARUP Laboratories	90[c] [12]	90[c] [12]
• pTau217	ALZpath	87[c] [13]	87[c] [13]
• pTau217	CertuitAD (Lilly SP-X)	91.2[c] [14]	90.4[c] [14]
• pTau217	Mayo Clinic Laboratories	92[c] [12]	96[c] [12]
• pTau217	Neurocode Labs	90.4[b], 94.5[c] [12]	92.6[b], 95.6[c] [12]
• P-Tau217/Np-Tau-217 ratio • Aβ42/Aβ40 ratio	PrecivityAD2	90[c] [12]	92[c] [12]
• Aβ42/Aβ40 • pTau217	Quest AD-Detect (Aβ42/Aβ40 pTau217)	87[b], 91[c] [12]	84[b], 91[c] [12]
• Aβ42/Aβ40 • pTau217 • ApoE	Quest	82[b], 91[c] [12]	93[b], 91[c] [12]
• Aβ42/Aβ40 ratio • pTau181 • NfL	Labcorp ATN Profile	89.6–96 for individual components [15]	68–86.7 for individual components [15]
• pTau 217 • Aβ42/40 • NfL • GFAP	LucentAD Complete	90[c] [12]	90[c] [12]
• pTau217/ß-Amyloid 1–42 ratio	Lumipulse G[e] (available from Labcorp)	97[c] [16]	92[c] [17]
• pTau 181	Elecsys pTau181[e] (available from Labcorp)	78[b] [13]	79[b] [13]

Abbreviations: GFAP, glial fibrillary acid protein; NfL, neurofilament light; pTau, phosphorylated tau.
[a]Pooled findings of several validation studies are available for some of the tests in reference [13].
[b]2-part readout, positive or negative.
[c]3-part readout using test-specific cut-points to interpret as negative, positive, or intermediate.
[d]Available direct-to-consumer for $412.
[e]FDA-approved, cost and medicare coverage are still pending.

for people who are interested in receiving anti-amyloid therapy or participating in clinical trials. A positive test can be the first step in initiating these processes. Although geriatricians and other primary care clinicians may not be directly involved in administering disease-modifying drugs, they should be prepared to discuss the risks and benefits of ordering diagnostic tests that might lead to these treatments, including prognosis with and without treatment. This approach is consistent with Alzheimer's Association Guidelines for use of these tests in specialty clinics [13] and the American Academy of Family Physicians statement on biomarkers [34].

It must also be recognized for blood-based biomarkers, the wheel's still in spin. The available tests are just the first generation and new blood-based biomarkers (e.g., MTBR-tau243) that are more specific for tau tangle pathology and correlate highly with tau scans [35] have been developed and will be marketed. With better understanding of the pathogenesis of Alzheimer's disease beyond the amyloid, tau, and neuronal pathway (e.g., the roles of inflammation and immune dysfunction, vascular dysfunction), new biomarkers may be developed. The clinical trials currently in progress may demonstrate that treating people with positive biomarkers who are cognitively unimpaired

may delay or prevent the development of Alzheimer's disease. Eventually, treatment of persons who have positive blood-based biomarkers may be comparable to treatment of persons with hypercholesterolemia. Because an estimated 90% of persons living with dementia are 65 years or older [36], geriatricians, including those currently in training, will need to keep current with the evolving status of diagnostic and therapeutic approaches to Alzheimer's disease and other causes of dementia through continuing education products and published reviews that address the risk and benefits of testing and treatment.

Until more is known, the decision whether to order blood-based biomarkers must meet the same risk–benefit threshold of all diagnostic tests: "will knowing the result benefit this patient?" If the result might change treatment, then the test is appropriate. If not, ordering is hard to justify based solely on the need to know [37].

Author Contributions

Each author contributed significantly to the work. **David B. Reuben:** conception and design, drafting the article and revising it critically for important intellectual content, and final approval of the version to be published. **Allison B. Chambliss:** drafting the article and revising it critically for important intellectual content, and final approval of the version to be published. **Bernard J. Katz:** drafting the article and revising it critically for important intellectual content, and final approval of the version to be published. **Alejandra Sánchez López:** drafting the article and revising it critically for important intellectual content, and final approval of the version to be published. **Jason D. Hinman:** drafting the article and revising it critically for important intellectual content, and final approval of the version to be published.

Conflicts of Interest

The authors declare no conflicts of interest.

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