



From Memory Tests to Molecular Signatures: How Blood Biomarkers Are Reshaping Alzheimer's Disease Diagnosis

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Opinion

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Abstract

The diagnosis of Alzheimer's disease is undergoing a fundamental change. For much of the modern era, clinicians have approached Alzheimer's disease primarily as a clinical syndrome, supported, when necessary, by cerebrospinal fluid analysis or amyloid positron-emission tomography. During 2024–2026, however, blood-based biomarkers have moved substantially closer to routine clinical use. Plasma phosphorylated tau, particularly p-tau217, has emerged as one of the most informative blood measures of Alzheimer's pathology, while new clinical guidance has begun to define when blood tests may be used for triage and when sufficiently accurate tests may substitute for amyloid PET or cerebrospinal fluid biomarkers in specialized care. This opinion article argues that the most important consequence of this development is not simply that a blood draw may replace a more complicated test. Rather, blood biomarkers have the potential to reorganize the patient journey: from an initially uncertain cognitive complaint toward earlier biological characterization, more rational treatment selection, and more efficient longitudinal monitoring. At the same time, enthusiasm must be balanced by assay variability, uncertainty in diverse populations, mixed pathology, and the danger of interpreting a biomarker without the clinical context in which it was obtained.

Keywords: Alzheimer's Disease; Blood-Based Biomarkers; Plasma P-Tau217; Molecular Diagnosis; Early Detection; Precision Medicine; Dementia

Introduction

Alzheimer's disease has traditionally been diagnosed by putting together several imperfect pieces of information. A patient may report progressive memory difficulty, a family member may describe changes in everyday function, cognitive testing may demonstrate impairment, and magnetic resonance imaging may reveal patterns of atrophy. None of these findings, on its own, establishes that Alzheimer's pathology is responsible. For many patients, biological confirmation has required either cerebrospinal fluid testing or amyloid PET, both of which are highly informative but

less accessible than routine blood testing. That situation is changing. The rapid development of plasma biomarkers has created a plausible route toward biological diagnosis using a conventional blood sample. The shift is especially important now because the emergence of disease-modifying therapies has made biological confirmation more than a research exercise. If treatment is directed at a specific pathological process, the clinical system needs practical ways to identify that pathology.

In 2024, expert groups were already proposing standardized pathways for incorporating blood-based

biomarkers into clinical practice. In 2025, the Alzheimer's Association published its first clinical practice guideline specifically addressing blood-based biomarker use in specialized care. The guideline did not recommend indiscriminate testing. Instead, it established performance thresholds and emphasized that biomarker results must be interpreted alongside clinical assessment and pretest probability [1,2]. This distinction is crucial. The arrival of blood biomarkers should strengthen diagnosis, not replace diagnostic reasoning.

Why the Blood-Biomarker Revolution Matters Now

The appeal of blood-based biomarkers is partly practical. Amyloid PET requires specialized imaging infrastructure, radiotracers, and considerable cost. Cerebrospinal fluid sampling is relatively inexpensive compared with PET but remains invasive and is not universally available. A blood test can potentially be performed in settings where neither modality is immediately feasible. The 2024 recommendations from the Global CEO Initiative on Alzheimer's Disease described two possible clinical pathways: a current pathway in which blood biomarkers are used to triage patients, and a future pathway in which sufficiently accurate tests could confirm amyloid pathology [2]. The rationale is closely connected to the expected increase in demand for biomarker testing as disease-modifying treatments become available. This is an important change in the logic of dementia care. Historically, clinicians could accept a degree of diagnostic uncertainty because treatment options were largely symptomatic. With disease-modifying treatment, uncertainty becomes more consequential. A patient and clinician may need to know whether Alzheimer's pathology is present, whether the disease is at an appropriate stage, and whether the expected benefits and risks of therapy justify treatment. Blood biomarkers therefore have the potential to reduce friction at precisely the point where the healthcare system is likely to experience greater demand.

Why p-Tau217 Has Become a Leading Candidate

Among the expanding group of blood biomarkers, phosphorylated tau has received particular attention. Several phosphorylated tau species have been studied, including p-tau181, p-tau231, and p-tau217. P-tau217 has become especially prominent because its relationship with Alzheimer's-related amyloid and tau pathology appears to provide strong discrimination between biologically defined Alzheimer's disease and several alternative conditions.

A large 2025 systematic review and meta-analysis by Therriault and colleagues evaluated plasma p-tau biomarkers across 113 studies involving 29,625 unique

individuals. The analysis reported pooled sensitivity of 88.1% and specificity of 88.7% for plasma p-tau217, with an area under the receiver operating characteristic curve of 91.1% [3]. Such findings explain why p-tau217 has moved quickly from an experimental marker toward a candidate for clinical implementation. But diagnostic accuracy should not be confused with clinical usefulness. A test can perform extremely well in a carefully selected research population and behave differently when used in an ordinary memory clinic. Real patients may have renal disease, vascular brain injury, Lewy body pathology, frontotemporal degeneration, or more than one pathological process. The question is therefore not simply, "Can p-tau217 identify Alzheimer's pathology?" It is also, "How should a clinician act when the p-tau217 result is inconsistent with the patient's presentation?" That second question is becoming more important as the technology moves into practice.

From a Biomarker Result to a Clinical Decision

The 2025 Alzheimer's Association guideline provides an important framework because it avoids treating all blood tests as equivalent. The guideline recommends that blood-based biomarker tests used for triage should achieve at least 90% sensitivity and 75% specificity. For a test to serve as a substitute for amyloid PET or cerebrospinal fluid biomarkers in specialized care, the recommended threshold rises to at least 90% sensitivity and 90% specificity [1]. This approach recognizes a basic principle of clinical diagnostics: the acceptable performance of a test depends on how the result will be used. A test intended to rule out Alzheimer's pathology can tolerate a different balance of errors than a test used to make a definitive biological classification. The guideline also emphasizes an issue that deserves more attention: the test is not merely the analyte. A blood-based biomarker result is produced by a specific analytical method, platform, laboratory process, and decision threshold. Two tests measuring the same biological target cannot automatically be assumed to have identical clinical performance. This has practical consequences. A clinician should not look at a numerical p-tau217 concentration in isolation and compare it with a cutoff taken from a different assay. Laboratory methods, calibration, units, and validated thresholds matter. The growing sophistication of blood biomarkers therefore creates a parallel need for greater laboratory literacy among clinicians.

Blood Biomarkers Do Not Make the Clinical Assessment Obsolete

There is a temptation to describe the blood test as the final step in the evolution of Alzheimer's diagnosis: a simple replacement for more complicated testing. That interpretation is attractive but misleading. A biomarker

answers a biological question. It does not answer every clinical question. A person may have a positive Alzheimer's biomarker and still have symptoms partly driven by vascular disease, medication effects, depression, sleep disorders, Lewy body disease, or another neurological condition. Conversely, an individual with progressive cognitive symptoms and an initially negative or borderline blood result may require additional investigation.

The 2025 guideline explicitly states that blood-based biomarkers should not replace comprehensive clinical evaluation and should be interpreted with consideration of pretest probability [1]. This provides the correct conceptual model for implementation. The best use of blood biomarkers is likely to be as an additional layer of information. Clinical assessment establishes the phenotype. Cognitive testing documents impairment. Imaging identifies structural or alternative pathology. Blood biomarkers contribute biological evidence. When these sources agree, diagnostic confidence rises. When they disagree, the disagreement itself becomes clinically informative and may justify additional investigation.

The Relationship with Amyloid PET and CSF

The arrival of high-performing blood tests does not mean that amyloid PET and cerebrospinal fluid testing have become obsolete. Instead, their roles may change. For many patients, blood biomarkers could become the first biological test. A clearly negative result from a validated high-performance assay might make further amyloid testing unnecessary. A clearly positive result might allow treatment planning to proceed in settings where the assay meets confirmatory performance requirements. Patients with borderline results, atypical presentations, or conflicting clinical information could still proceed to PET or CSF. This model has an important advantage: it uses expensive or invasive resources selectively. Rather than asking every patient to undergo the same diagnostic sequence, the system could reserve advanced testing for the cases in which it is most informative. There is also a research advantage. Blood biomarkers could make it easier to identify potential participants for prevention and disease-modifying treatment studies. They may also permit repeated measurements with less burden than repeated CSF sampling or PET imaging.

However, blood testing should not be assumed to capture every aspect of disease biology. Amyloid positivity, tau burden, neurodegeneration, vascular injury, and other coexisting processes are not interchangeable. A patient-centred diagnostic pathway will continue to need multiple forms of evidence in selected cases.

The 2024–2026 Shift Toward Earlier and More Actionable Diagnosis One of the most consequential developments of the current period is that diagnosis and treatment are becoming increasingly connected. The 2024 implementation recommendations explicitly linked scalable blood biomarker pathways to the anticipated demand created by disease-modifying treatments [2]. This changes the meaning of “early diagnosis.” Earlier diagnosis is valuable not only because patients and families may benefit from understanding the cause of symptoms. It may also determine whether an individual is evaluated at a stage when a disease-modifying therapy could reasonably be considered.

At the same time, this creates a risk of overdiagnosis if biological information is interpreted without sufficient clinical context. The more actionable a test becomes, the more important its false-positive and false-negative consequences become. The field should therefore resist the idea that faster testing is automatically better care. The goal should be faster access to the right information. In some patients, that will be a blood test. In others, it will be blood testing followed by PET or CSF. In still others, the most appropriate response may be to investigate a non-Alzheimer's explanation for cognitive symptoms.

Real-World Challenges

Research cohorts often provide ideal conditions for biomarker development. Participants may be carefully phenotype, samples may be collected under standardized protocols, and the prevalence of Alzheimer's pathology may differ from that in general clinical practice. Real-world populations are more complicated. They include people with multimorbidity, atypical symptoms, uncertain disease duration, different educational backgrounds, diverse genetic backgrounds, and varying access to specialist care. The 2024 implementation literature specifically highlighted the need for community-based studies and better understanding of biomarker performance across diverse populations [4]. There is also a systems problem. Introducing blood biomarkers requires laboratory capacity, quality assurance, clinician training, reporting standards, reimbursement mechanisms, and patient education. If one part of this pathway is weak, the apparent simplicity of the blood test can become misleading. Equity deserves particular attention. A test may be inexpensive relative to PET, but it is not automatically equitable. Availability of validated assays, specialist interpretation, confirmatory testing, and treatment will vary across health systems and countries. A successful implementation strategy must consider the entire pathway rather than the price of the initial blood draw.

A More Mature View of Biomarker Precision

The most useful way to think about the current generation of biomarkers is not as isolated diagnostic labels but as components of a molecular profile. The emerging biological framework recognizes amyloid, tau, neurodegeneration, and other pathological processes as related but distinct dimensions. Blood tests may eventually contribute information about several of these processes. For example, plasma p-tau can provide information related to AD-specific tau biology, while neurofilament light reflects more general neuronal injury and GFAP may provide information related to astrocytic activation. This does not mean that a larger panel is automatically a better panel. Additional biomarkers should be adopted when they answer a meaningful clinical question. A test that provides another number without changing diagnosis, prognosis, or management may increase complexity without improving care. The coming years should therefore focus on clinical utility rather than biomarker accumulation. The critical question is whether a biomarker changes what clinicians do and whether that change benefits patients.

Clinical Implications

For specialized memory services, the most immediate implication is the possibility of establishing a structured blood-first diagnostic pathway. Patients with objective cognitive impairment and a clinical suspicion of Alzheimer's disease could undergo a validated blood-based biomarker test before more invasive or expensive procedures are considered.

A positive result should be interpreted according to the validated assay and clinical context, not as an isolated diagnosis. A negative result may reduce the likelihood of Alzheimer's pathology when the test has sufficient sensitivity, while an uncertain result can identify patients who would benefit from PET or CSF confirmation. The approach could reduce diagnostic delays and make biological assessment more accessible. It could also help clinicians identify patients who should be evaluated for disease-modifying treatment. Importantly, the same implementation pathway should include mechanisms for discussing uncertainty with patients and families rather than presenting biomarker results as absolute predictions.

Challenges and Limitations

The central limitation of the current evidence is that diagnostic performance and clinical utility are not the same thing. Much of the evidence base has been generated in research settings with carefully characterized participants. Broader populations may produce different performance.

Assay heterogeneity is another major concern. Different analytical technologies can produce different results, and a cutoff validated for one method cannot automatically be transferred to another. This makes standardization and transparent reporting essential. Mixed pathology creates a further challenge. Alzheimer's pathology frequently coexists with vascular lesions, Lewy body pathology, and other age-associated changes. A positive AD biomarker therefore does not establish that Alzheimer's disease is the sole cause of cognitive impairment. Finally, implementation may widen rather than reduce disparities if high-performing assays and confirmatory testing remain concentrated in specialist centres. The field needs evidence from different healthcare systems and populations before claiming universal applicability.

Future Directions

The next stage of research should move beyond another series of retrospective accuracy comparisons. Prospective implementation studies are needed to determine whether blood-based testing actually improves patient outcomes and healthcare efficiency. Important questions include how blood testing changes time to diagnosis, how often it avoids PET or CSF, how clinicians respond to discordant results, whether it improves access to disease-modifying treatment, and whether patients understand the meaning of biomarker results. Standardization should remain a priority. Laboratories need reliable reference materials, validated analytical methods, transparent reporting, and quality-control systems. Studies should also recruit participants from diverse populations and ordinary clinical settings. Another important direction is longitudinal use. If blood biomarkers can reliably track biological change, they may eventually become useful for monitoring disease progression or treatment response. However, that application requires separate validation; diagnostic accuracy at one time point does not establish suitability for longitudinal monitoring. Finally, future clinical pathways should integrate biomarkers with cognition, imaging, genetics, and functional measures rather than assuming that one laboratory result can summarize a complex neurodegenerative disease.

Conclusion

The blood-biomarker era represents one of the most consequential changes in Alzheimer's disease diagnosis in recent years. The significance of p-tau217 and related biomarkers is not simply that they offer a convenient alternative to PET or CSF. Their deeper importance is that they make biological characterization more scalable at a time when diagnosis is becoming increasingly connected to disease-modifying treatment. The evidence available through 2024–2026 supports cautious optimism. Performance is

strong for several validated assays, and the 2025 Alzheimer's Association guideline provides a practical framework for distinguishing triage from confirmatory use. Yet the field is not finished. Real-world validation, assay standardization, diverse populations, clinical workflow, and equitable access remain unresolved. The most useful future is therefore not a "blood test instead of clinical medicine" model. It is a more intelligent diagnostic pathway in which a validated blood biomarker provides an early molecular signal, clinicians interpret that signal in context, and PET or CSF remains available when uncertainty demands greater resolution. If implemented in that way, blood biomarkers could make Alzheimer's diagnosis not only easier, but timelier, more biologically grounded, and ultimately more useful to patients.

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