



When a Blood Test Replaces a PET Scan: The Emerging Clinical Role of Alzheimer's Blood Biomarkers

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Abstract

The rapid development of blood-based biomarkers has created a practical question for Alzheimer's disease care: when can a blood test provide enough biological information to make amyloid positron-emission tomography (PET) or cerebrospinal fluid (CSF) testing unnecessary? The question has become more urgent as disease-modifying therapies have made biological confirmation clinically consequential. Evidence published during 2024–2026 indicates that high-performing plasma biomarkers can approach the diagnostic information obtained from established amyloid biomarkers in selected populations. Prospective primary- and secondary-care data, real-world memory-clinic studies, and biomarker–PET concordance studies all support a blood-first strategy. Yet substitution should not be interpreted as universal replacement. Assay-specific performance, pretest probability, kidney function, atypical clinical phenotypes, mixed pathology, and discordant results remain important. This short communication proposes a tiered diagnostic pathway in which validated blood biomarkers are used to answer the simplest biological question first, while PET and CSF are retained for cases in which greater resolution or confirmation is needed.

Keywords: Alzheimer's Disease; Blood Biomarkers; Amyloid PET; Cerebrospinal Fluid; P-Tau217; Diagnostic Pathway; Clinical Implementation

The Question Has Changed

For years, the practical question in Alzheimer's disease diagnosis was whether clinicians should obtain cerebrospinal fluid biomarkers or amyloid PET when clinical assessment suggested Alzheimer's disease. The emergence of high-performing blood biomarkers changes the question. The issue is now whether every patient who needs biological confirmation should undergo PET or lumbar puncture at all. This is not a purely technological debate. PET and CSF have established biological validity, but they

require infrastructure, specialist expertise, or an invasive procedure. A blood sample is considerably easier to obtain and can potentially be collected repeatedly. If a validated plasma biomarker can identify Alzheimer's pathology with sufficiently high accuracy, insisting on PET or CSF for every patient may represent an inefficient use of clinical resources.

The 2025 Alzheimer's Association Clinical Practice Guideline directly addresses this issue. It recommends that blood-based biomarker tests achieving at least 90% sensitivity and 75% specificity can be used for triage, while

tests reaching at least 90% sensitivity and specificity may substitute for amyloid PET or CSF biomarkers in patients with cognitive impairment evaluated in specialized memory care [1]. The language is important: substitution is conditional, performance-based, and restricted to the appropriate clinical setting.

Evidence From Prospective Clinical Care

One of the strongest arguments for changing the diagnostic pathway comes from prospective evidence rather than retrospective research cohorts. In a large study of 1,213 patients undergoing evaluation for cognitive symptoms in Sweden, plasma biomarkers were evaluated in primary and secondary care using predefined cutoff values established in an independent cohort [2]. The investigators examined the percentage of plasma p-tau217 and an amyloid probability score incorporating plasma amyloid-beta 42/40. In prospective testing, diagnostic accuracy was approximately 90% across both primary and secondary care cohorts. The amyloid probability score achieved an area under the curve of 0.96 in primary care and 0.97 in secondary care. Importantly, the study also compared biomarker performance with clinical diagnosis. The blood test substantially outperformed clinical assessment alone for identifying AD pathology [2]. The relevance of this finding is practical. It suggests that a carefully validated blood-based pathway can work outside a highly selected research population. It does not prove that every blood assay is equally accurate, but it demonstrates that the concept of blood-first diagnosis can be tested prospectively in ordinary clinical pathways.

What PET Still Does Better

The argument for blood-first diagnosis should not become an argument against PET. Amyloid PET provides direct visualization of amyloid burden and can answer questions that a blood concentration cannot. PET may be particularly valuable when the clinical phenotype is atypical, when blood results fall into an intermediate range, or when there is a substantial discrepancy between clinical findings and biomarker results. It can also be important in research protocols requiring precise characterization of amyloid burden. A blood biomarker is fundamentally a probability-generating test. PET provides spatial information and an established pathological reference. The two modalities therefore answer related but not identical questions. The more sensible future is to reserve PET for the situations in which its additional information changes management. A patient with a typical amnesic syndrome and a high-confidence positive result from a guideline-level blood assay may gain little from an additional PET scan. A patient with an unusual syndrome and a borderline plasma result may gain a great deal.

What CSF Still Contributes

CSF remains a highly informative biological modality because it provides direct measurement of amyloid-beta and tau-related biomarkers in the central nervous system. It can be especially useful when blood testing is inconclusive or when a more comprehensive biomarker profile is required. There are also circumstances in which CSF may be more informative than a single plasma analyte. A patient with a complex or atypical presentation may benefit from simultaneous assessment of amyloid-beta ratios, phosphorylated tau, and other markers of neuronal injury. Nevertheless, lumbar puncture is not equally acceptable or accessible to every patient. Some individuals have contraindications, anxiety about the procedure, or limited access to experienced clinicians. For these patients, a validated blood-based test could provide an important first biological assessment. The appropriate question is therefore not whether CSF is obsolete. It is whether every patient should be exposed to an invasive test when a validated non-invasive alternative can answer the immediate clinical question. Increasingly, the evidence suggests that the answer is no.

The Problem of Discordant Results

The most difficult patients in a blood-first pathway will not be those with clearly positive or clearly negative results. They will be the patients in the middle. A biomarker may be borderline. A blood result may indicate Alzheimer's pathology while the clinical presentation strongly suggests another disease. Kidney dysfunction may elevate plasma p-tau217 in a patient without Alzheimer's pathology. A patient may also have genuine Alzheimer's pathology together with vascular or Lewy body disease. Recent outpatient memory-clinic data illustrate this issue. In a tertiary-care cohort of 509 patients, plasma p-tau217 showed 95% sensitivity and 82% specificity for symptomatic AD. Adding plasma A β 42 to form a p-tau217/A β 42 measure increased specificity to 86%. The investigators also observed that reduced kidney function was associated with higher plasma p-tau217 and p-tau217/A β 42 concentrations in patients who did not have AD according to CSF biomarkers [3]. This is precisely the type of situation in which PET or CSF retains value. A blood-first system should not be designed to eliminate second-line testing. It should be designed to identify which patients genuinely need it.

A Tiered Diagnostic Model

A practical pathway can be imagined as three stages. The first stage would be clinical assessment. The patient would undergo history-taking, cognitive evaluation, neurological examination, and appropriate structural imaging. This establishes the phenotype and determines

whether Alzheimer's disease is sufficiently plausible to justify biological testing. The second stage would be a validated blood-based biomarker. A result clearly below a validated negative threshold could reduce the probability of AD pathology. A result clearly above a validated positive threshold could provide biological confirmation when the assay meets the performance requirements for substitution. Patients falling between thresholds would proceed to additional testing. The third stage would be confirmatory or advanced testing. PET or CSF would be used when the blood result is indeterminate, the clinical picture is atypical, the patient has factors that may affect biomarker interpretation, or treatment decisions require additional certainty. This structure has a major advantage: it treats uncertainty as an expected feature of diagnosis rather than a failure of the test.

Why Pretest Probability Matters

A blood test does not operate in a vacuum. The probability that a patient has Alzheimer's pathology before testing changes the meaning of the result. Consider two patients with identical plasma biomarker values. One has progressive amnesic MCI, hippocampal atrophy, and no strong alternative diagnosis. The other has rapidly progressive behavioural change, prominent hallucinations, parkinsonism, and severe vascular disease. The same laboratory result should not necessarily lead to the same clinical conclusion. The 2025 guideline explicitly cautions that blood biomarkers should be interpreted with consideration of pretest probability and should not substitute for comprehensive clinical evaluation [1]. This is particularly important if testing expands beyond specialist memory clinics. A highly accurate biomarker used indiscriminately in a low-prevalence population can produce more false-positive findings than clinicians expect. This is one reason why the first wave of clinical implementation should occur in settings where trained clinicians can integrate the result with a complete assessment.

The Importance of Assay-Specific Performance

Another reason to be cautious about the phrase "blood test" is that there is no single blood test. Commercial and research platforms differ in analyte definition, antibodies, calibration, sample preparation, analytical sensitivity, and reporting. The 2025 guideline was deliberately brand-agnostic but emphasized that many commercially available blood-based tests do not meet the recommended thresholds, particularly when a single cutoff is used [1]. This is a crucial safeguard against the assumption that a promising biomarker automatically becomes a validated clinical test. Pre-analytical factors also matter. A 2025 best-practice guideline from the National Alzheimer's Coordinating Centre–Alzheimer's Disease Research Centre biomarker community emphasized the importance of standardized

collection, processing, storage, and reporting of blood and CSF specimens [4]. A blood-first pathway will therefore succeed only if laboratory quality accompanies clinical enthusiasm. A technically simple blood draw can still generate an unreliable result if the analytical pathway is not standardized.

Implications for Disease-Modifying Treatment

The practical urgency of biomarker substitution has increased because anti-amyloid therapies require biological evidence of appropriate pathology. A slow diagnostic pathway can become a barrier to treatment when patients are eligible only within a particular stage of disease. A 2026 study examining interchangeability between plasma biomarkers and amyloid PET found that plasma p-tau217 had 90.1% overall agreement with florbetapir PET and a positive predictive value of 88.0% for PET positivity in the studied population [5]. The investigators concluded that blood-based tests showed promise for identifying patients who may benefit from amyloid-targeting therapy. These findings do not mean that every patient receiving therapy should bypass PET or CSF. Instead, they strengthen the case for using validated blood biomarkers as an efficient entry point into the treatment pathway. If the blood result is sufficiently reliable, the patient may move more rapidly toward eligibility assessment. If uncertainty remains, PET or CSF can provide the additional evidence required.

Clinical Implications

The most immediate clinical implication is a reduction in unnecessary invasive or expensive testing. A blood-first strategy could allow memory clinics to reserve PET and lumbar puncture for patients with uncertain results or atypical clinical presentations. This could shorten waiting lists, reduce diagnostic burden, and potentially make biological diagnosis available in regions where PET is not practical. It may also support earlier discussion of disease-modifying therapies. However, the pathway should be accompanied by standardized reporting. Laboratory reports should identify the assay used, validated thresholds, and any important interpretive limitations. Clinicians should have access to a defined second-line pathway for discordant or intermediate results. Most importantly, the patient should be told what the result means—and what it does not mean. A positive blood biomarker indicates evidence of Alzheimer's biology; it does not predict an exact future course or establish that every symptom is caused by AD.

Limitations and Unresolved Issues

Several questions remain before blood biomarkers can routinely replace PET or CSF across healthcare systems.

First, the strongest evidence is still concentrated in specialized cohorts and specific assays. Second, many studies use different reference standards and cutoff strategies. Third, real-world patients often have comorbidities that are less common in research cohorts. Renal dysfunction is one example. The recent memory-clinic study showed that reduced kidney function can raise plasma p-tau217 concentrations in patients without AD pathology [3]. Such findings do not invalidate the biomarker, but they demonstrate why interpretation requires patient-level context. There is also uncertainty about populations outside the settings in which the assays were validated. Differences in age, ethnicity, genetics, comorbidity, and healthcare pathways may affect clinical performance. Finally, replacing PET or CSF is not merely a diagnostic decision. It changes resource allocation, treatment pathways, patient expectations, and potentially the management of uncertainty. Implementation should therefore be evaluated as a healthcare intervention, not only as a laboratory test.

Future Directions

The next research priority should be prospective pathway studies. Instead of asking only whether p-tau217 correlates with amyloid PET, researchers should ask what happens when clinicians actually receive the result. Does blood-first testing shorten time to diagnosis? How many PET scans are avoided? How many lumbar punctures are avoided? How often do clinicians disagree with the blood result? Does blood-guided diagnosis increase appropriate access to disease-modifying treatment? Do patients understand the result? These are clinical-utility questions, and they are now more important than another isolated accuracy estimate. Research should also evaluate adaptive pathways using two thresholds. Patients with clearly low results could avoid additional testing, patients with clearly high results could proceed according to treatment eligibility protocols, and those in the intermediate zone could undergo PET or CSF. Finally, global implementation should be studied deliberately. The value of a blood test will be greatest where PET and CSF access is limited, but those settings are also where laboratory infrastructure and specialist expertise may be less available. Implementation science will therefore be as important as biomarker science.

Conclusion

The arrival of high-performing blood biomarkers does

not make amyloid PET and cerebrospinal fluid obsolete. It changes when they are needed. Evidence from prospective primary- and secondary-care cohorts, real-world memory clinics, and biomarker-PET concordance studies increasingly support a blood-first approach for appropriately selected patients. The 2025 Alzheimer's Association guideline provides a practical framework by separating triage tests from assays accurate enough to substitute for PET or CSF in specialized care [1,2]. The most defensible future is therefore a tiered model. Clinical assessment comes first. A validated blood biomarker provides a scalable biological checkpoint. PET or CSF remains available when the result is intermediate, the phenotype is atypical, or additional biological resolution is necessary. Such a model does not represent the disappearance of PET or CSF. It represents a more rational allocation of them. The goal should not be to eliminate established tests. It should be to stop using the most burdensome test when a validated, clinically appropriate alternative can answer the same question with sufficient confidence.

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