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# SELECTED BLOOD-BASED BIOMARKERS IN ALZHEIMER'S DISEASE: CLINICAL APPLICATIONS, DIAGNOSTIC UTILITY, AND IMPLEMENTATION CHALLENGES

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**ABSTRACT**

**Background:** Alzheimer's disease (AD) poses major public health challenges. Traditional CSF and PET diagnostics are invasive, expensive, and limited in routine practice, driving the need for accessible plasma biomarkers.
**Objectives:** To evaluate the diagnostic and prognostic utility of key plasma biomarkers (plasma Aβ42/Aβ40 ratio, p-tau species, NfL, t-tau, GFAP, sTREM2) and identify limitations to their clinical implementation.
**Methods:** A structured literature search was conducted in the PubMed database for English-language clinical studies and review articles published between October 2007 and June 2026. Keywords and MeSH terms included "Alzheimer's disease", "blood-based biomarkers", "immunoprecipitation-mass spectrometry (IP-MS)", and "mild cognitive impairment". Studies focusing on adult clinical biomarkers underwent a narrative synthesis.
**Results:** Plasma Aβ42/Aβ40 and p-tau species (p-tau181, p-tau231, p-tau217) reliably detect early amyloid pathology and differentiate AD from other dementias. NfL, GFAP, and sTREM2 track axonal damage, astrogliosis, and microglial activity, facilitating disease monitoring and therapeutic response assessment. However, clinical translation is constrained by demographic variations, somatic comorbidities, and a lack of standardized multi-marker reference ranges.
**Conclusions:** Plasma biomarkers offer a transformative, non-invasive approach to early AD diagnosis and primary care triage, reducing reliance on CSF and PET scans. Overcoming demographic and methodological limitations is essential for their widespread clinical adoption.

**KEYWORDS**

Alzheimer's Disease, Blood-Based Biomarkers, Mild Cognitive Impairment, Immunoprecipitation-Mass Spectrometry (IP-MS)

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## Introduction

Alzheimer's disease (AD) is the leading cause of dementia and progressive cognitive decline in older adults worldwide [1]. Its incidence has risen in recent years, mainly due to an aging population and higher rates among women. This trend has created major public health challenges, including increased socio-economic burdens and delays in making an accurate diagnosis [1,2].

In recent years, diagnostic criteria have evolved to better recognize degenerative changes in patients with dementia symptoms or even in those at a preclinical stage with genetic risk factors. This shift moves diagnosis away from relying only on clinical symptoms and post-mortem confirmation, and toward modern *in vivo* biological tests that can detect key disease processes, such as beta-amyloid and tau protein buildup or disturbances in signaling pathways [3,4].

Classic diagnostic methods based on cerebrospinal fluid (CSF) analysis and positron emission tomography (PET) are important for appraising these changes. However, their use in everyday practice is limited because lumbar puncture is invasive, the procedures are expensive, and the necessary equipment is not always available [3,4]

Knowledge regarding plasma biomarkers in Alzheimer's disease is analyzed to assess their clinical potential as an easily accessible alternative and to discuss the primary implementation barriers associated with their broad application in diagnostics [3,5].

## Methods

A structured literature search was conducted to identify studies investigating novel blood-based biomarkers in Alzheimer's Disease. The search was performed using the PubMed database and limited to articles published in English between October 2007 and June 2026. The search strategy utilized combinations of keywords and Medical Subject Headings (MeSH) terms, including "Alzheimer's disease", "blood-based biomarkers", "immunoprecipitation-mass spectrometry (IP-MS)", and "mild cognitive impairment". Literature selection focused primarily on clinical studies and review articles focusing on clinical biomarkers in adults. The gathered literature underwent a narrative synthesis to emphasize its diagnostic utility, prognostic value, and current limitations in clinical application.

## Plasma Aβ42/Aβ40 Ratio

The plasma Aβ42/Aβ40 ratio currently represents one of the most important blood-based biomarkers in neurology and Alzheimer's disease diagnostics.

The Aβ42 peptide differs structurally from Aβ40 by the presence of two additional hydrophobic amino acids at the C-terminus, which is responsible for its high neurotoxicity and propensity for rapid oligomerization [1]. The monomeric form of Aβ40 exhibits a protective effect in solution, modulating the kinetic stability and solubility of Aβ42 aggregates while inhibiting their transformation into mature amyloid fibrils [2].

In peripheral circulation, Aβ40 and Aβ42 peptides bind to modified low-density lipoproteins, thereby stimulating lipid uptake and accelerating macrophage foam cell formation [3]. The reduction of the plasma Aβ42/Aβ40 ratio directly stems from the sequestration and entrapment of Aβ42 molecules within developing amyloid plaques in brain tissue [4].

Longitudinal studies have demonstrated that a decline in plasma levels of Aβ42 and Aβ40 correlates with the progression of cognitive impairment and the risk of conversion to fully symptomatic Alzheimer's disease [5]. Measurement of the plasma Aβ42/Aβ40 ratio allows for the identification of cerebral amyloid pathology in individuals at a preclinical, entirely asymptomatic stage of disease development [4]. Plasma Aβ42/Aβ40 ratio values display a highly significant correlation with cerebrospinal fluid amyloid concentrations and amyloid PET neuroimaging findings [6]. This assay facilitates highly precise diagnostics during early symptomatic stages as well as in patients with mild cognitive impairment, thereby streamlining patient qualification for novel disease-modifying therapies [6]. Advanced diagnostic tests combining mass spectrometry for plasma Aβ42/Aβ40 ratio measurement with ApoE proteotyping and patient age enable highly accurate determination of brain amyloid status [7].

Plasma Aβ42/Aβ40 biomarkers measured in blood samples represent a minimally invasive, broadly accessible, and cost-effective alternative to far more invasive lumbar punctures—which carry an increased risk of complications during cerebrospinal fluid collection—and expensive PET scans in routine clinical practice [7].

## Phosphorylated Tau Species (p-tau181, p-tau231, p-tau217)

The p-tau231 isoform demonstrates high sensitivity to early amyloid plaque accumulation and functions as a state marker during the preclinical phase [8]. Blood plasma concentrations of p-tau181 rise markedly in individuals with cognitive impairment [9]. The p-tau217 isoform is recognized as a reliable indicator of amyloid pathology and neurostructural alterations in the brain [10].

Clinical studies indicate that quantifying p-tau181, p-tau217, and p-tau231 yields high diagnostic accuracy in differentiating Alzheimer's disease from both healthy controls and individuals with mild cognitive impairment [11]. Measurement of plasma p-tau217 and p-tau181 allows for precise distinction between Alzheimer's disease and other neurodegenerative disorders, including frontotemporal dementia [12]. Additionally, plasma p-tau217 measurement supports the detection of amyloid pathology in patients with concurrent cerebrovascular alterations [13].

The adoption of blood tests for p-tau217 in clinical settings substantially enhances diagnostic accuracy and increases physician confidence in clinical decision-making [14]. Utilization of plasma p-tau217 testing in memory clinics demonstrates high diagnostic value in the early stages of Alzheimer's disease [15]. Measurement of plasma p-tau217 levels is crucial for identifying suitable candidates for novel amyloid-lowering immunotherapies [16]. Evidence from diverse populations affirms the broad clinical applicability of plasma p-tau217 as an accessible and non-invasive diagnostic modality [17].

**Neurofilament Light Chain (NfL) and Total Tau (t-tau)**

Neurofilaments are important proteins in the neuronal cytoskeleton, and neurofilament light chains (NfL) are crucial for keeping axons stable and maintaining their diameter [23]. In normal conditions, NfL helps stabilize the microtubule network and supports proper axonal transport in the nervous system [23].

Plasma NfL levels gradually rise as patients move from normal cognition to subjective cognitive decline (SCD), then to mild cognitive impairment (MCI), and finally to dementia caused by Alzheimer's disease (AD) [24].

Measuring plasma NfL in people with SCD and MCI helps identify those at higher risk of progressing quickly to dementia [25]. Plasma NfL levels clearly relate to how severe cognitive deficits are, as measured by the ADAS-cog scale and other tests [26]. Studies show that NfL levels increase over time and reflect how quickly brain tissue is lost in Alzheimer's patients [27]. However, high serum NfL is not unique to Alzheimer's disease and can indicate axonal damage in other neurological conditions as well [28].

For this reason, NfL works well as a general marker of neurodegeneration in advanced biomarker systems (like ATNIVS) and is useful in clinical trials to measure how treatments slow neuronal loss [29,30]. Plasma NfL levels can also be affected by vascular problems, such as cerebral small vessel disease (CSVD), so it is important to combine biomarker tests with neuroimaging studies [31]. Logically stabilizes the cytoskeletal framework in neurons and is responsible for proper nerve impulse conduction [23].

Total tau present in biofluids reflects the overall intensity of neuronal damage. The amount of total tau in body fluids indicates how much neuronal damage and acute neurodegeneration are occurring in the brain [30]. While plasma t-tau levels are much higher in Alzheimer's patients than in healthy people, measuring t-tau alone is not specific enough for diagnosis [26]. Long-term monitoring of AD progression due to intra-individual variability and lower dynamic changes over time [27]. The high measurement variance of plasma t-tau also means that utilizing it as an endpoint in clinical trials requires analyzing significantly larger sample sizes compared to NfL [30]. In clinical practice, significant heterogeneity in the t-tau profile is observed in patients undergoing novel anti-amyloid therapies (such as lecanemab), highlighting the need to combine it with other, more specific biomarkers [29].

**GFAP and TREM2**

Glial fibrillary acidic protein, or GFAP, basically works as the core structural framework within astrocytes. It keeps their shape intact, holds the blood-brain barrier together, and gives neural tissue the physical support it needs [32].

Well before any obvious symptoms of Alzheimer's actually show up, high GFAP levels in blood samples start trending inversely with β-amyloid markers. This suggests that astrocytes are drawn into the amyloid cascade much earlier than we used to think [33]. Checking these GFAP levels helps us get a clearer picture of where someone's cognition is headed, mostly because higher initial values tend to signal a faster drop in attention span for people sitting in high-risk categories for dementia [34].

In clinical settings, measuring plasma GFAP gives doctors a remarkably sensitive—and thankfully non-invasive—way to support early differential diagnosis and monitor reactive astrogliosis [35]. Moving toward blood tests means patients can skip uncomfortable procedures like lumbar punctures for spinal fluid, which makes screening people for clinical trials way easier [36]. Plus, tracking GFAP lets us see how body-wide immune responses talk to brain inflammation within what researchers call the immuno-glial connectome [37].

On the other hand, TREM2 acts as a membrane receptor found almost exclusively on microglia. Its job is to detect lipids, clear protein debris through phagocytosis, and keep these key immune cells alive [37].

In the quiet, preclinical phase of Alzheimer's, seeing more of its soluble version (sTREM2) usually goes along with rising levels of phosphorylated tau and synaptic damage markers [33]. Yet, a higher starting point for sTREM2 in cerebrospinal fluid is linked to a slower decline in memory and executive skills, suggesting that a properly activated microglial response might defend the brain [34].

In real-world medical settings, sTREM2 levels offer a solid readout for gauging neuroinflammation and microglial activity as dementia progresses through different stages [35]. Researchers also use this protein as an endpoint when testing new immunomodulatory drugs designed to activate the TREM2 pathway in Alzheimer's patients [36]. Getting a better grasp of how TREM2 signaling connects with astrocytic markers gives us a front-row seat to how microglia and astrocytes interact as neurodegeneration unfolds [32].

**Table 1.** Diagnostic Main Advantages and Limitations of Key Blood-Based Biomarkers for Alzheimer's Disease

| Marker | What It Detects/Associated with | Status/Main Advantage | Main Limitations |
|---|---|---|---|
| Aβ42/Aβ40 | Formation of amyloid plaques in the brain (amyloid pathology) | Gold standard for early detection. Detects changes 10–20+ years before the onset of clinical symptoms. | Plasma ratio drop is subtle (~10–15%), requiring high-precision assays<br>High pre-analytical sensitivity (stickiness to plastic tubes) |
| p–tau181, p-tau217, p-tau231 | Hyperphosphorylated tau protein forming neurofibrillary tangles inside neurons. | High specificity for Alzheimer's. Excellent for differentiating Alzheimer's disease from other forms of dementia (blood-based variants offer exceptionally high accuracy). | Assay availability varies by region/platform<br>Plasma levels can be altered by chronic kidney disease (CKD)<br>Less informative for non-AD tauopathies |
| NfL *(Neurofilament light chain)* | Axonal damage and breakdown (neuronal death). | Universal marker of neurodegeneration dynamics. Ideal for monitoring disease progression and assessing structural brain damage (not specific to Alzheimer's alone). | Non-specific (elevated in stroke, trauma, MS, ALS, normal aging)<br>Cannot differentiate between underlying disease etiologies |
| GFAP | Astrocyte activation (reactive neuroinflammation in response to amyloid). | Earliest indicator of neuroinflammatory response. Highly reliable in blood plasma tests, showing changes at the very early stages of amyloid pathology. | Non-specific (elevated in stroke, trauma, MS, ALS, normal aging)<br>Cannot differentiate between underlying disease etiologies |
| sTREM2 | Microglial activation (the brain's immune system response to pathology). | Marker of microglial response. Useful for evaluating neuroinflammation levels and the brain's innate defense mechanisms during the disease process. | Complex temporal pattern (levels fluctuate dynamically across disease stages)<br>Blood-CSF correlation is weaker; less established in routine clinical settings |
| t-tau *(Total tau)* | General, acute neuronal damage and cell death. | Indicator of the rate of neuronal destruction. A traditional cerebrospinal fluid (CSF) marker; spikes rapidly in acute conditions like strokes of Creutzfeldt-Jakob disease. | Poor performance in plasma due to fast peripheral breakdown/clearance<br>Lacks AD specificity compared to p-tau species |

**Immunoprecipitation-Mass Spectrometry (IP-MS) as a Novel Method for Determining Plasma Biomarkers in Alzheimer's Disease**

Recently, in the diagnostics of plasma biomarkers for Alzheimer's disease, traditional laboratory methods have been replaced by novel, ultrasensitive technologies such as immunoprecipitation-mass spectrometry (IP-MS), which combines the initial selective capture and enrichment of target proteins using antibodies with their subsequent precise analysis via mass spectrometry. Mass spectrometry-based methods demonstrate very high reliability and analytical precision, achieving the highest accuracy among all tested platforms in comparative studies [39].

Integration of the immunoprecipitation-mass spectrometry (IP-MS) method with liquid chromatography-mass spectrometry (LC-MS) enables highly precise quantification of the amyloid A**β**42/A**β**40 ratio in plasma. When adjusted for patient age and APOE gene status, the A**β**42/A**β**40 ratio measured by this approach exhibits superior predictive performance for brain amyloid deposition [39]..

Mass spectrometry-based blood tests enable early, non-invasive detection of Alzheimer's disease pathology. Applying this method helps limit the need for invasive lumbar punctures to collect cerebrospinal fluid and reduces the necessity for costly PET imaging scans. This technology is widely used in clinical trials for patient qualification and to evaluate the efficacy of new drugs. Based on the LC-MS method, commercial laboratory tests available in clinical practice have already been developed, such as PrecivityAD™ and Quest AD-Detect™. Unfortunately, each method has certain limitations, which in this case include high equipment costs and limited availability [39].

**Clinical Use of Plasma Biomarkers for the Diagnosis and Management of Alzheimer's Disease**

Plasma biomarker measurement in primary care enables the early and non-invasive identification of patients at increased risk of Alzheimer's pathology [38]. Using blood tests for selection (triage) allows distinguishing cognitive impairment caused by Alzheimer's disease from changes resulting from other causes [38]. Implementing these markers in the general practitioner's office significantly reduces unnecessary referrals for advanced and hard-to-access specialized diagnostic procedures [38]. The availability of blood tests helps quickly select patients who will benefit most from referral to a neurologist and further diagnostic workup [38].

Regarding the use of plasma biomarkers in treatment, they serve as crucial indicators for evaluating the biological response to anti-amyloid therapies, such as donanemab or lecanemab [39]. Administering drugs that clear amyloid plaques leads to a marked reduction in plasma phosphorylated tau levels (e.g., p-tau181, p-tau217), reflecting a decline in the intensity of brain tau and amyloid pathology [39]. Conversely, a drop in plasma neurofilament light chain (NfL) levels indicates a slowing of neurodegenerative processes and axonal damage under effective treatment [38]. The rapid response of plasma p-tau markers to administered therapies makes them an excellent tool for tracking treatment efficacy without the need for repeated invasive lumbar punctures or PET scans [39].

Recommendations from international societies, such as the Alzheimer's Association, increasingly support the integration of plasma biomarkers into diagnostic criteria and clinical practice [38]. Blood tests are securing FDA approvals and Breakthrough Device designations, accelerating their adoption into widespread commercial use [38]. However, experts emphasize that guidelines urge caution, recommending plasma p-tau and p-tau/Aβ markers as supportive tests that should be interpreted alongside the patient's clinical symptoms [38]. Progress in assay standardization enables the development of consistent regulatory guidelines, facilitating the broad use of blood testing to qualify patients for new DMT therapies [39].

**Clinical and Methodological Limitations of Blood-Based Biomarkers**

Unfortunately, nothing is perfect, and utilizing plasma biomarkers in the diagnosis of Alzheimer's disease carries certain limitations as well as specific methodological and clinical challenges.

A main limitation of blood-based biomarkers, such as pTau-181 or pTau-217, is their considerable variability depending on the patient's race and ethnicity [40]. Plasma concentrations of these proteins tend to be noticeably higher in Caucasian individuals than in African American individuals who are at the same clinical stage of the disease [40]. Moreover, the historical insufficient representation of minority groups in scientific research creates a major knowledge gap regarding the actual effectiveness of plasma tests in the general population [41].

Psychosocial stress and environmental elements also influence blood biomarker levels [42]. Consequently, elevated plasma biomarker levels do not always reflect underlying neurodegenerative pathology alone, which heavily complicates the interpretation of results [42]. Additionally, socioeconomic factors or

education levels further change biomarker concentrations and cognitive status, serving as significant confounding variables [43].

One must not overlook multimorbidity in older adults, which likewise contributes to uncertain test outcomes. These include somatic and cardiometabolic conditions, such as diabetes, hypertension, hypercholesterolemia, or neoplastic diseases [40]. The high prevalence of metabolic and vascular disorders distorts the relationship between blood biomarker levels and actual brain status [43].

If we use individual plasma biomarkers, we must take into account that they feature limited accuracy when differentiating mild cognitive impairment (MCI) from full-blown dementia [40]. Blood test results do not always correspond to advanced brain imaging, and positivity rates in amyloid PET scans show marked differences with plasma indicators depending on the cohort analyzed [43]. Therefore, it would be best to create multi-marker diagnostic models that account for sex, age, education, or genetic variants, which currently poses a major challenge [40]. Developing population-specific reference ranges and continuing test validation throughout all ethnic groups are essential steps to prevent misdiagnoses in routine clinical practice [40]; [41].

**Conclusions**

The plasma biomarkers discussed in this review represent a significant, non-invasive, and cost-effective advancement in neurological diagnostics. These biomarkers enable the detection of amyloid plaque pathology and neuronal damage during the extended preclinical phase of Alzheimer's disease [9; 12; 13].

Quantifying these proteins in blood samples enables precise differentiation of Alzheimer's disease from other dementias. Additionally, these measurements provide real-time insights into axonal damage and glial cell responses, underscoring their broad clinical utility [17; 23; 32].

General adoption of these biomarkers requires addressing methodological challenges, including the effects of comorbidities and population variability [40]. Nevertheless, these biomarkers are poised to shape the future of neurological medicine. Their integration into primary care settings is expected to transform cognitive screening, reduce reliance on invasive lumbar punctures, and facilitate early, large-scale identification of candidates for novel targeted disease-modifying therapies [21; 38; 39].

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