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Review Article

Advancing Early Detection in Alzheimer's Disease: Clinical Utility and Implementation of Plasma Biomarkers.

Himank Patel*, Asefa Chauhan

Bachelor of pharmacy, SAL Institute of Pharmacy.

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by β amyloid [Aβ] plaque deposition and hyperphosphorylated tau (p-Tau) neurofibrillary tangles. While cerebrospinal fluid (CSF) analysis and positron emission tomography (PET) are established diagnostic tools, their high cost, invasive nature, and limited accessibility restrict routine clinical screening. This narrative review evaluates the clinical role, analytical techniques, and implementation challenges of blood-based biomarkers (BBMs) for AD diagnosis, staging, and therapeutic monitoring. Plasma Aβ42/ Aβ40 ratios detect early amyloid deposition, acting as an effective pre-screened. Phosphorylated tau species—specifically p-Tau181, p-Tau217, and p-Tau231—demonstrate high specificity for AD pathology and correlate with disease severity, with p-Tau217 achieving diagnostic accuracy exceeding 90% (AUC > 0.90). Markers of neurodegeneration, such as Neurofilament Light Chain (NFL), and astroglia activation, such as Glial Fibrillary Acidic Protein (GFAP), track progressive neuronal injury and neuroinflammation. Furthermore, blood biomarkers enable the early identification of eligible candidates for disease-modifying monoclonal antibody therapies (e.g., lecanemab, donanemab) and provide objective pharmacodynamic metrics to monitor treatment response. Advanced platforms, including Single Molecule Array (Simoa), fully automated chemiluminescent enzyme immunoassays (Lumipulse), and Immuno-precipitation–Mass Spectrometry (IP-MS), provide the analytical sensitivity required to measure low peripheral biomarker concentrations. However, clinical translation is constrained by pre-analytical variability, a lack of standardized cut-off thresholds, inter-platform inconsistencies, limited validation in demographically diverse populations, and ethical considerations surrounding early risk disclosure.

***Corresponding Author:** Himank Patel
Address: Bachelor of pharmacy, SAL Institute of Pharmacy.
Email ✉: himank.patel153@gmail.com
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INTRODUCTION:

Alzheimer's disease (AD) is a complex neurodegenerative disorder, already impacting millions worldwide, and it is anticipated to reach markedly higher prevalence by mid-century due to global demographic shifts. Accounting for 60–70% of dementia cases, AD is marked by progressive cognitive and functional decline, with patients experiencing memory loss, impaired executive functions, behavioural changes, and, ultimately, a complete loss of independence.[1] Seizures are up to seven times more common in people with dementia compared with peers of the same age, while falls that cause injury are two to three times more common for people living with dementia, potentially leading to reduced mobility and quality of life.[2]

The identification of accurate and early biomarkers for AD is a critical focus of current research, as early diagnosis and intervention are essential for altering the disease's course and enhancing patient outcomes.[3] The pathophysiology of AD is driven by the accumulation of β-amyloid (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau (p-Tau) protein.[4] These aggregates disrupt neuronal communication and trigger neuronal loss, particularly in brain regions critical for memory and cognition, such as the medial temporal lobe and more specifically the hippocampus.[5]

AD diagnosis has relied on clinical assessment, supplemented by confirmatory tests such as cerebrospinal fluid (CSF) analysis and positron emission tomography (PET) imaging to detect amyloid and tau pathology.[6] Even if these methods are accurate and well established. their high costs and limited accessibility restrict their routinary use in primary care and large-scale screening.

The ATN classification system is a biological framework created by the National Institute on Aging and the Alzheimer's Association (NIA-AA) to define Alzheimer's disease by its underlying pathology rather than clinical symptoms. The A/T/N Categories divides core biomarkers into three binary (positive or negative) categories. **A (Amyloid-beta):** Measures amyloid deposition using amyloid PET scans or cerebrospinal fluid (CSF) $A\beta_{42}$. **T (Tau):** Measures pathologic tau protein using CSF phospho-tau (p-tau) or tau PET imaging. **N (Neurodegeneration):** Measures neuronal injury or degeneration using [18F]-fluorodeoxyglucose (FDG)-PET, structural MRI (brain atrophy), or CSF total tau.[7]

The updated ATN criteria are now more flexible and inclusive. They officially recognize fluid and imaging biomarkers while adding blood tests to the diagnostic guidelines for the first time. This update reflects growing evidence that blood tests—measuring Aβ isoforms, p-Tau (like p-Tau181 and p-Tau217), and NFL—can accurately reflect brain changes that previously required spinal taps or brain scans.

The revised ATN system maintains its tripartite structure but now allows clinicians and researchers to select the most appropriate and accessible biomarker modalities for each category, depending on available resources, patient characteristics, and the clinical context.[8]

The 2024 revision reaffirms that the ATN framework defines Alzheimer's disease by biology—brain changes like amyloid, tau, and nerve damage—rather than noticeable symptoms. Under this biological model, Alzheimer's is viewed as a continuous process. It begins before any memory loss appears, progresses to mild cognitive impairment, and eventually advances to full dementia.[9]

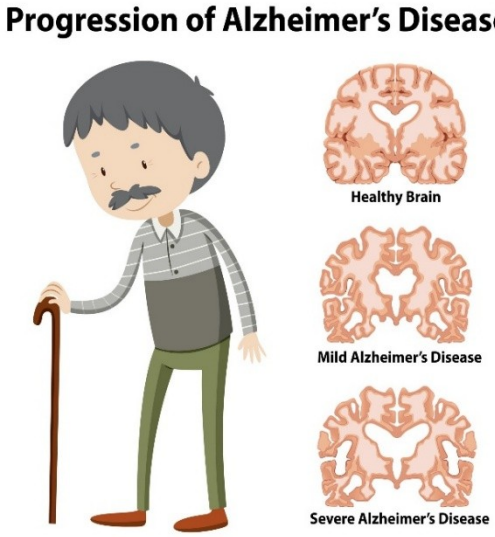

Figure 1: [9]

In addition, the 2024 update provides clearer guidelines for handling conflicting biomarker results and stresses the need for long-term monitoring, as a patient's ATN

status can change over time. The revised framework also highlights how ATN profiling helps doctors select appropriate disease-modifying therapies (DMTs) that target specific disease mechanisms. Overall, these updated guidelines will help integrate fast, accessible blood tests into routine clinical practice, leading to more personalized Alzheimer's diagnosis and treatment.[10]

Blood-based biomarkers have emerged as a transformative alternative to current diagnostic procedures, offering a minimally invasive, accessible, and cost-effective solution for screening, early detection, and longitudinal monitoring.[11][12] Advanced lab techniques (such as ultrasensitive immunoassays, Simoa, mass spectrometry, and automated systems like Lumipulse) can now measure extremely low concentrations of Alzheimer's biomarkers (Aβ, p-Tau, and NFL) in blood with high sensitivity and precision.[13] Disease-modifying monoclonal antibodies targeting amyloid plaques (such as lecanemab and donanemab) make early diagnosis essential. Because these drugs prevent plaque accumulation rather than reversing late-stage damage, their clinical efficacy relies on identifying eligible patients at the earliest stage of the disease.[14] Blood-based biomarkers are thus poised to play a crucial role in patient selection, monitoring therapeutic response, and advancing personalized medicine in AD.[15]

This narrative review examines current blood-based biomarkers for Alzheimer's disease, covering their biological mechanisms and clinical diagnostic value. It evaluates major hurdles—including assay standardization, analytical variability between testing platforms, demographic diversity, and ethical issues—and outlines future strategies for adopting blood tests into routine medical practice and clinical trials.

BLOOD BIOMARKERS IN ALZIMER'S DISEASE

AMYLOID B:

Amyloid-beta (Aβ) peptides—especially Aβ40 and Aβ42—are the main cause of Alzheimer's disease (AD) and form the core idea behind how the disease develops (the amyloid cascade hypothesis).[16] These peptides are generated from the amyloid precursor protein (APP) through sequential cleavage by β-secretase (BACE1) and γ-secretase.[17] An imbalance between Aβ production and clearance leads to the oligomerization and deposition of Aβ42 into extracellular plaques, which disrupt neuronal communication, promote oxidative stress, activate microglia, and ultimately contribute to synaptic dysfunction and neuronal death.[4] Amyloid-beta (Aβ) starts building up in the brain up to 20 years before any clear symptoms show up, making it one of the earliest signs of Alzheimer's disease.[18] The ratio of Aβ42/40 in cerebrospinal fluid has served as a reliable biomarker of cerebral amyloid burden, correlating strongly with amyloid PET imaging.[6] CSF collection via lumbar puncture is relatively invasive and impractical for large-scale screening or routine clinical use. This is particularly true in elderly patients, who represent the primary population affected by AD. In this group, lumbar puncture poses additional challenges due to age-related physiological changes such as decreased cerebrospinal fluid flow and altered CSF composition, which can complicate sample collection and interpretation. Moreover, elderly patients often have comorbidities, frailty, and spinal degenerative changes that increase the risk of procedural complications and patient discomfort. The procedure may also be contraindicated in individuals taking anticoagulants or those with bleeding disorders, as the risk of spinal hematoma is elevated. Because lumbar punctures are risky and hard to perform in elderly patients, researchers have focused on developing blood tests for Aβ. A simple blood draw is a much safer and less painful (less invasive) alternative that can be easily used for routine screening.[19]

The development of blood-based assays for Aβ has thus been a major goal, offering a Patient-friendly and accessible alternative.

Historically, detecting Aβ in plasma was challenging due to its low abundance, peripheral metabolism, and binding to carrier proteins, such as albumin and lipoproteins, which limited both sensitivity and specificity.[20] Recent technological advances have transformed this landscape. Immunoprecipitation-mass spectrometry (IP-MS) and single molecule array platforms now enable the sensitive and specific quantification of plasma Aβ42/Aβ40 ratios.[21] Large cohort studies, including ADNI, BioFINDER, and AIBL, have

demonstrated that plasma Aβ42/40 correlate with amyloid PET status, supporting its use as a non-invasive diagnostic tool.[22] Studies show that measuring blood Aβ42/Aβ40 levels using IP-MS can accurately identify patients with Alzheimer's plaques (with over 88% accuracy) and predict the disease up to eight years before symptoms appear.[23][24] AUC is the key indicator of diagnostic accuracy in a Receiver Operator Characteristic (ROC) analysis conducted to compare different diagnostic tests. The AUC value reflects the accuracy of a test in distinguishing two populations (e.g., healthy controls and patients), and it ranges from 0.50, when population differentiation is random, to 1, when the two populations are perfectly recognized and separated by the studied test.[25] Even with these new techniques, blood Aβ tests face challenges because a person's results can be altered by kidney health, blood vessel issues, inflammation, or genetic factors like the APOE-ε4 gene.[26] The difference in blood Aβ levels between healthy people and Alzheimer's patients is very small, which makes it hard to spot the disease early using a blood test alone. Therefore, Aβ tests work best when combined with other blood biomarkers instead of being used on their own.[27]



Figure 2: Amyloid-*beta Plaque* Formation and Blood Biomarker Testing.[28]

Right now, blood Aβ42/Aβ40 tests can be used in clinical trials to pre-screen patients, assess risk, and act as a first filter before performing expensive brain PET scans or spinal taps [in CSF]. Because it detects brain changes years before symptoms start, it is ideal for early screening and starting early preventive treatment. [18] To use blood Aβ tests widely in clinics and research, scientists must standardize testing methods, set clear reference threshold values, and correct for patient health factors that alter test results.

TAU PROTEINS:

Tau proteins are integral to neuronal function, playing a vital role in stabilizing microtubules and maintaining axonal integrity, which are in turn essential for intracellular transport and neuronal communication.[29] In Alzheimer's Disease (AD), **tau**—a protein that normally stabilizes brain cell structures—gets overloaded with phosphate groups (**hyperphosphorylation**). Because of this structural change: **Tau detaches** from microtubules, disrupting the cell's internal transport system. **Tau misfolds and clumps together** inside neurons, forming **neurofibrillary tangles (NFTs)** that block cell function and eventually cause cell death.[30] These tangles (**NFTs**) are a major physical sign of Alzheimer's in the brain. As they build up, they disrupt communication between neurons (**synaptic dysfunction**) and directly lead to memory loss and thinking problems (**cognitive decline**) [5]. Tau pathology spreads through the brain in a predictable anatomical sequence mapped out by Braak staging: **Initial stage (Braak I–II):** Tangles start in the **entorhinal cortex** (memory pathway hub). **Intermediate stage (Braak III–IV):** Progression into the **hippocampus** (core memory formation centre). **Advanced stage (Braak V –VI):** Widespread distribution across the **neocortex** (outer layer controlling higher-level thinking and reasoning).[31]

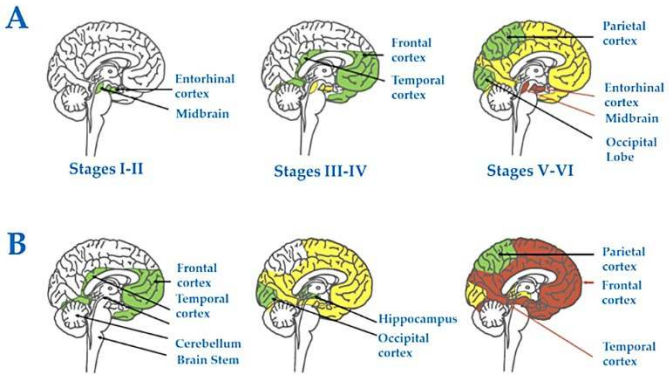

Figure 3: Braak Staging of Tau Pathology in Alzheimer's Disease.[32]

This predictable pattern correlates with the clinical progression of cognitive symptoms, underscoring the central role of Tau in disease evolution.

In recent years, phosphorylated tau isoforms detectable in blood have emerged as valuable biomarkers for AD diagnosis, disease monitoring, and therapeutic evaluation.[33] As for many other biomarkers, blood levels of phosphorylated Tau isoforms should be integrated in a comprehensive approach that also includes clinical evaluation, neuroimaging, and other laboratory tests. Given that plasma p-Tau can be elevated in other neurological and neuromuscular conditions, such a multidimensional protocol is essential to ensure an accurate diagnosis and avoid misclassification. Indeed, a recent study highlights that p-Tau increases are not exclusive to AD pathology, but can also occur in amyotrophic lateral sclerosis (ALS) and certain myopathies.[34] Relying on blood p-tau levels alone creates a significant risk of **false-positive diagnoses**. Because p-tau can also rise due to other conditions (e.g., acute stroke, traumatic brain injury, or neuromuscular diseases like ALS), accurate Alzheimer's diagnosis requires a **comprehensive diagnostic strategy, Neurological Examination:** Assessing motor skills, reflexes, and coordination to rule out non-AD movement or neuromuscular disorders. **Detailed Clinical History:** Reviewing the onset, progression, and pattern of cognitive decline alongside cardiovascular/head trauma history. **Complementary Investigations:** Combining blood results with neuroimaging (MRI/PET) and cognitive testing to confirm Alzheimer's pathology before initiating treatment.

Among the various phosphorylated tau species, p-Tau181 is widely validated; its concentrations in blood plasma tightly mirror both CSF p-Tau181 levels and tau-PET neuroimaging, offering an accurate measure of CNS tau burden.[35] Importantly, p-Tau181 levels begin to rise early in the disease continuum, including during the preclinical phase, when cognitive symptoms are not yet evident. This early increase allows p-Tau181 to discriminate AD from other neurodegenerative dementias, such as frontotemporal dementia (FTD), with a diagnostic accuracy often reflected by AUC values exceeding 0.85.[36][37] longitudinal studies have demonstrated that rising plasma p-Tau181 levels predict cognitive decline and the progression from mild cognitive impairment (MCI) to overt dementia, highlighting its prognostic value.[38] More recently, plasma **p-Tau217** has emerged as a preferred isoform over p-Tau181, demonstrating higher diagnostic accuracy and greater specificity for Alzheimer's disease.[39] This isoform more effectively distinguishes AD from other tauopathies, including progressive supranuclear palsy (PSP) and frontotemporal dementia (FTD).[40] For example, clinical studies demonstrate that plasma **p-Tau217** aligns more strongly with amyloid and tau-PET imaging than key CSF assays, attaining an AUC > 0.90 when distinguishing Alzheimer's patients from healthy controls.[41][42] The enhanced diagnostic specificity of plasma **p-Tau217** has driven its widespread implementation in Alzheimer's drug development (e.g., TRAILBLAZER-ALZ), functioning simultaneously for candidate selection and therapeutic response monitoring.[43][44] Another promising biomarker, p-Tau231, is gaining recognition as an ultra-early indicator of AD pathology. Unlike p-Tau181 and p-Tau217, p-Tau231 levels rise even before tau PET imaging becomes positive, reflecting the earliest molecular changes induced

by amyloid accumulation and tau misprocessing.[45][46] **p-Tau231** is rising as an important early biomarker; its ability to detect early cognitive loss and positive amyloid scans in prodromal AD makes it ideal for early patient screening and preventive therapy.[47] Supporting this, a recent head-to-head study comparing plasma and cerebrospinal fluid p-Tau217, p-Tau181, and p-Tau231 in a memory clinic cohort demonstrated that while plasma p-Tau217 showed the highest overall diagnostic accuracy, plasma p-Tau231 was particularly sensitive in identifying early amyloid pathology, highlighting its value as a biomarker for the earliest stages of AD progression.[48]

Integrated into clinical research as both screening criteria and surrogate outcome measures, these p-tau biomarkers offer invaluable, real-time tracking of tau pathology during the development and testing of novel Alzheimer's therapies.[39]

Notwithstanding the immense potential of plasma p-tau species, key obstacles hamper their routine clinical implementation—most notably inter-assay variability caused by differing testing platforms, reagents, and analytical protocols, which impedes data cross-comparison between laboratories. Additionally, there is a lack of universally accepted standardized cut-off values, which limits clinical interpretability and decision-making.[49] Another critical limitation is the underrepresentation of diverse populations in biomarker validation studies; most research to date has focused on relatively homogeneous cohorts, often lacking sufficient inclusion of non-white and underserved groups. This gap raises concerns about the generalizability and equity of biomarker-based diagnostics.[50] Resolving these implementation barriers requires ongoing global efforts toward assay harmonization, multi-population clinical validation, and the creation of standardized clinical interpretation frameworks.[51] Such initiatives are essential to fully harness the potential of plasma p-Tau biomarkers in advancing precision medicine approaches for AD, ultimately enabling earlier diagnosis, improved patient stratification, and more effective therapeutic monitoring.

NEUROFILAMENT LIGHT CHAIN:

Neurofilament light chain is a structural cytoskeletal protein predominantly found in large, myelinated axons, where it supports axonal caliber and conduction velocity.[52] Upon neuronal injury, NFL is released into the interstitial fluid and subsequently diffuses into cerebrospinal fluid and blood.[53] high levels of NfL in the blood act as a sensitive biomarker that signals ongoing nerve cell damage or brain degeneration across various neurological conditions (such as Multiple Sclerosis, Alzheimer's, or Parkinson's disease).[54,55,56]

In AD, plasma NFL concentrations progressively increase with disease severity and correlate with key indicators of neurodegeneration, including hippocampal atrophy and global brain volume loss on MRI, and cognitive decline.[57,58] Long-term studies show that blood NFL levels start rising years before any symptoms of Alzheimer's Disease (AD) actually show up. In inherited (familial) cases of AD, elevated plasma NFL can be detected 10 to 15 years before the patient is expected to develop memory loss or cognitive symptoms.[59] Additionally, blood NFL levels can predict whether a patient with Mild Cognitive Impairment (MCI) will progress to full Alzheimer's dementia, while closely reflecting structural brain loss on MRI scans and worsening mental performance.

Despite its sensitivity, NFL lacks specificity for AD, as elevated levels are also observed in other central nervous system diseases, such as ALS, multiple sclerosis, vascular dementia, traumatic brain injury, and various neuroinflammatory conditions.[60] Additionally, factors like aging, vascular risk, and comorbidities can influence plasma NFL levels, further complicating interpretation. Therefore, NFL is most informative when combined with disease-specific biomarkers, such as β-amyloid and p-Tau, to improve diagnostic accuracy.[27]

Hence, the dosage of plasmatic NFL levels is extensively used in various clinical scenarios, and is often combined with other biomarkers when the suspicion of a neurodegenerative disorder rises. Moreover, the utility of NFL in the management of AD patients extends beyond the diagnostic phase, since it has been proposed as a marker of therapeutic response in clinical trials.[61,62] serial plasma NFL measurements could in fact

contribute to longitudinal monitoring of neurodegeneration over time.

Recent advances in mass spectrometry have further refined the characterization of NFL proteoforms in plasma, enhancing our understanding of its molecular complexity, and providing potential for improved biomarker development and performance.[63] However, challenges remain, including assay standardization, definition of robust clinical cut-offs, and validation across diverse populations.[64]

GLIAL FIBRILLARY ACID PROTEIN:

Glial fibrillary acidic protein (GFAP) is an intermediate filament protein predominantly expressed by astrocytes that serves as a marker of astrogliosis and neuroinflammation, processes now recognized as early and critical components of AD pathophysiology.[65] Elevated plasma GFAP levels reflect astrocyte activation and correlate strongly with both amyloid burdens, measured by PET imaging, and cognitive decline.[66]

Emerging research shows that blood GFAP levels become abnormal earlier than tau biomarkers, making it a key candidate for the very early detection of Alzheimer's Disease (AD).[67] Studies have shown that plasma GFAP discriminates amyloid-positive from amyloid-negative individuals with a high sensitivity, particularly in asymptomatic or prodromal stages.[68] it has been demonstrated that GFAP outperforms neurofilament light chain and some tau biomarkers in distinguishing amyloid status.

Longitudinal data reveals that plasma GFAP levels rise up to a decade before the onset of cognitive impairment and remain elevated through disease progression.[69] Studies have shown that blood GFAP levels can predict whether a patient with Mild Cognitive Impairment (MCI) will progress to Alzheimer's dementia.[68] This early rise in blood GFAP is likely caused by astrocytes reacting to amyloid-beta (Aβ) plaques combined with a weakened blood–brain barrier (BBB), which allows GFAP to leak into the bloodstream during the early (prodromal) stage of Alzheimer's Disease.

However, although brain-specific, GFAP is not AD-specific, since elevated levels are also observed in other neurological conditions, such as traumatic brain injury, multiple sclerosis, and stroke, and can also be influenced by systemic inflammation.

Therefore, it is advisable to include GFAP in multi-biomarker panels, alongside disease-specific biomarkers, in order to maximize its diagnostic and prognostic utility and interpret results through a more comprehensive perspective.[27]

Recent meta-analyses and large cohort studies confirm the clinical potential of blood GFAP measurements to improve early diagnosis of AD and disease monitoring.[22,68,70]

neuroinflammation is increasingly recognized as a key target for disease-modifying therapies, blood GFAP levels are now being evaluated in clinical trials as a pharmacodynamic (PD) marker to measure how well treatments suppress glial cell activation.[68]

An overview of the main aspects of plasma biomarker is available in Table 1.

Table 1: Overview of Established Blood Biomarkers in Alzheimer's Disease.

Blood Biomarker	Biological Role	Detection Method	Diagnostic Utility	Limitations	References
Aβ42/Aβ40	Reflects amyloid plaque formation and deposition	Simoa, IP-MS, Lumipulse	Early detection of amyloid pathology; correlates with amyloid PET; useful in preclinical stages	Low plasma abundance; peripheral metabolism confounds levels; assay variability across platforms	[23,71]

Blood Biomarker	Biological Role	Detection Method	Diagnostic Utility	Limitations	References
p-Tau181, p-Tau217, p-Tau231	Reflect amyloid and tau pathology	Simoa, IP-MS, Lumipulse	Specificity for AD; distinguishes AD from other dementias; early and prodromal stage detection; prognostic for progression	Inter-assay variability; need for standardized cut-offs; emerging data for p-Tau231	[35,36,72]
NFL	Marker of axonal injury and neurodegeneration	Simoa, IP-MS, Lumipulse	Tracks disease progression; prognostic value for cognitive decline	Not specific to AD; elevated in other neurodegenerative diseases and with aging; influenced by comorbidities	[73,74]
GFAP	Astrocytic activation and gliosis	Simoa, IP-MS, Lumipulse	Early marker of astroglial activation; correlates with amyloid pathology; predictive of cognitive decline	Elevated in other neurological conditions; assay standardization needed	[75]

OTHER INFLAMMATORY BIOMARKERS:

Neuroinflammation has been recognized as a core driving factor in the development and progression of Alzheimer's Disease (AD), closely linked with the traditional disease hallmarks: amyloid-beta (Aβ) plaque buildup and tau protein tangle formation.[4] This inflammatory process involves a continuous interaction between activated microglia, reactive astrocytes, and the release of inflammatory signalling molecules (cytokines and chemokines). Far from being a passive byproduct, neuroinflammation actively worsens brain damage and accelerates Alzheimer's progression—creating a vicious cycle that multiplies amyloid and tau pathology, destroys synapses, and speeds up neuron death.[5]

In recent years, several inflammatory biomarkers detectable in blood have been identified as potential indicators of neuroinflammatory response in AD.[76] Although these markers are generally nonspecific, and thus less suitable for independent evaluation, they hold considerable promise for monitoring disease progression and therapeutic response. Among these, YKL-40 (chitinase-3-like protein 1 or CHI3L1) is one of the most studied.[77] Primarily secreted by astrocytes and microglia, elevated levels of YKL-40 in both plasma and cerebrospinal fluid reflect glial activation and correlate strongly with tau pathology and cognitive decline. Importantly, YKL-40 levels tend to increase progressively along the AD continuum, making it a valuable candidate for staging disease severity and tracking neuroinflammatory activity over time.[71]

Another important biomarker is soluble TREM2 (sTREM2), a protein fragment shed from the surface of microglia (the brain's immune cells). Levels of sTREM2 in the blood (plasma) and spinal fluid (CSF) rise significantly during the early symptomatic stages of Alzheimer's, representing a **protective,** compensatory attempt by microglia to clear toxic amyloid plaques.[72] This biomarker is particularly sensitive in the late preclinical phase, reflecting microglial activation before overt clinical symptoms manifest. Its dynamic changes offer insights into the evolving neuroimmune landscape of AD and provide a window into microglial function and dysfunction.[73]

Pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β) are frequently found at elevated levels in AD patients, indicative of both systemic and central nervous system inflammation.[74] However, their clinical utility as diagnostic markers is limited by considerable variability and notable lack of specificity, as these cytokines are elevated in numerous other inflammatory and infectious conditions.

The advent of multiplex proteomic platforms, such as Olink and SomaScan[75], has revolutionized the ability to quantify dozens to hundreds of inflammatory proteins simultaneously in plasma samples. These high-throughput technologies have uncovered distinct inflammatory signatures associated with different stages of AD and varying cognitive trajectories. While individual inflammatory markers alone cannot pinpoint Alzheimer's Disease (AD), combining them into multi-marker blood panels alongside core AD biomarkers significantly improves diagnostic accuracy, enabling earlier detection and far more precise tracking of disease progression.[27]

Longitudinal studies have further demonstrated that plasma levels of YKL-40, and sTREM2 increase progressively from preclinical to symptomatic stages of AD.[78] Beyond their diagnostic and prognostic roles, these neuroinflammatory biomarkers offer significant value in clinical trials, particularly for evaluating novel anti-inflammatory or glial-targeting disease-modifying therapies (DMTs). They offer minimally invasive tools to monitor therapeutic response and disease progression, complementing imaging biomarkers, such as translocator protein (TSPO) and monoamine oxidase B (MAO-B) PET tracers, which visualize glial activation in vivo.[4] This multimodal approach enhances the ability to assess target engagement and treatment efficacy in real time.

Despite their potential, the clinical application of neuroinflammatory blood biomarkers faces challenges, primarily due to their nonspecific nature.[78] Because elevated levels of YKL-40, sTREM2, and GFAP also occur in other neurological conditions (such as stroke, multiple sclerosis, and traumatic brain injury), they must be measured as part of a broader, multi-biomarker panel to prevent diagnostic misinterpretation and false positives.

OTHER EMERGING BIOMARKERS:

Beyond established biomarkers of amyloid-beta (Aβ), tau, neurodegeneration, and neuroinflammation, current research focuses on novel plasma biomarkers that capture additional aspects of Alzheimer's Disease (AD) pathophysiology. These emerging blood-based markers reflect biological processes including synaptic loss, oxidative stress, metabolic dysregulation, and proteostasis impairment, offering a comprehensive view of the complex biological landscape of AD.

Synaptic dysfunction represents one of the earliest pathological events in AD, often preceding overt neuronal loss and clinical symptoms. Plasma levels of synaptic proteins, including neurogranin, synaptosomal-associated protein 25 (SNAP-25), and synaptotagmin, have been shown to correlate with synaptic integrity and cognitive performance.[79,80,81] These synaptic proteins serve as sensitive indicators of synaptic health, offering functional insights into brain performance that go beyond what structural MRI or general neurodegeneration markers (like NFL) can reveal. Consequently, they are emerging as promising biomarkers for early detection and tracking disease progression in Alzheimer's Disease (AD).

Oxidative stress is another hallmark of AD pathology, driven largely by mitochondrial dysfunction and the accumulation of reactive oxygen species.[5] This leads to widespread cellular damage, including lipid peroxidation, DNA oxidation, and protein modification. Several oxidative stress markers, such as 8-hydroxy-2′-deoxyguanosine (8-OHdG), malondialdehyde (MDA), and F2-isoprostanes, have been found elevated in the plasma of AD patients.[82,83,84,85] Despite their clear biological relevance, problems with assay standardization, reproducibility across laboratories, and analytical sensitivity have slowed the transition of these novel biomarkers into routine clinical practice, highlighting the need for further testing refinement.

Metabolomic and lipidomic profiling have revealed consistent alterations in amino acid and lipid metabolism in individuals with AD. [86] Changes in blood plasma levels of specific fats and energy molecules—specifically phosphatidylcholines, ceramides, and acylcarnitine's—have been identified in research studies. These distinct metabolic signatures help separate Alzheimer's Disease (AD) patients from healthy individuals and point to ultra-early metabolic dysregulation that occurs before memory loss or cognitive symptoms begin.[87] These metabolic signatures not only enhance diagnostic accuracy, but also provide valuable insights into disease mechanisms, including mitochondrial

dysfunction and altered lipid homeostasis, which may serve as therapeutic targets.[88]

Proteostasis dysfunction—the failure of cellular protein folding, trafficking, and clearance mechanisms—is a central feature of Alzheimer's Disease (AD) that drives toxic protein aggregation. Blood-derived neuron-derived extracellular vesicles (NDEVs), or exosomes, overcome the challenge of peripheral blood dilution by acting as a non-invasive "liquid brain biopsy." They isolate and transport CNS-specific proteins—including Aβ, phosphorylated tau (p-tau), synaptic markers, and misfolded protein debris—directly from neurons into the bloodstream.[89] Exosomal tau phosphorylated at multiple sites has demonstrated high diagnostic accuracy and shows potential for early detection and prediction of cognitive decline, making exosome analysis a particularly exciting frontier in biomarker research.[90]

Recent advances in high-throughput proteomic technologies (such as Mass Spectrometry, Olink, and SomaScan) have accelerated the discovery of novel plasma biomarkers across diverse clinical populations. [91], Key novel findings include Brain-Derived Neurotrophic Factor (BDNF) as an indicator of neuronal plasticity, alongside clear evidence that genetic risk factors—specifically the [APOE]epsilon4-genotype—directly influence the expression levels of synaptic and fluid biomarkers.

However, numerous inflammatory and vascular-related proteins have also been linked to demographic factors, such as age, race, and sex, emphasizing the need to consider population diversity in biomarker research and interpretation.

Innovative approaches targeting proteins involved in endothelial cell migration and vascular remodelling reflect an important paradigm shift: Alzheimer's Disease (AD) is not solely a neurodegenerative disorder, but a neurovascular disease driven in part by cerebrovascular dysfunction.[92]

Although these emerging biomarkers hold great promise, they largely remain in the discovery or early validation stages. To transition from research to clinical application, extensive longitudinal studies in multiethnic cohorts are essential to establish their robustness, reproducibility, and generalizability.[93] Assay standardization and integration with established Alzheimer's Disease (AD) biomarkers are crucial to ensure diagnostic accuracy and clinical utility. The future of AD diagnostics lies in sophisticated multianalyte blood panels that combine novel emerging markers with classical biomarkers, leveraging machine learning (ML) and systems biology approaches to enhance early detection, disease prognostication, and personalized treatment strategies.[94]

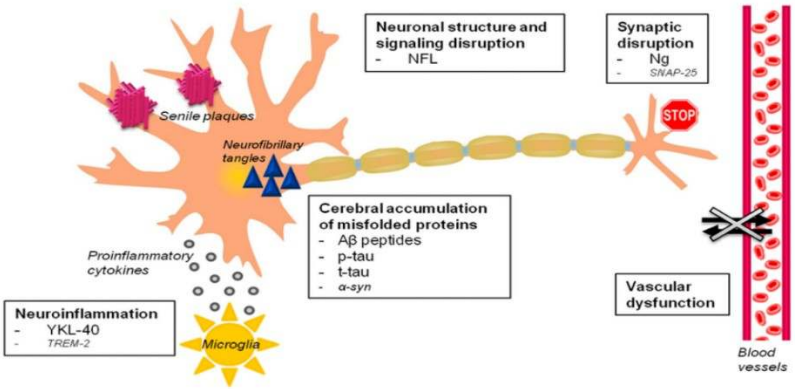

Figure 4: Major Pathophysiological Processes and Fluid Biomarkers in Alzheimer's Disease.[95]

Table 2. summarizes the principal characteristics of emerging blood biomarkers, focusing on those related to neuroinflammation, synaptic impairment, oxidative stress and metabolic alterations.

Table 2: Emerging Blood Biomarkers in Alzheimer's Disease: Biological Roles, Detection, and Clinical Relevance.

Biomarker	Biological Role	Detection Method(s)	Current Evidence	Limitations	References
Neuro-inflammation YKL-40, sTREM2, IL-6, TNF-α, IL-1β	Markers of astrocyte and microglial activation; mediators of systemic and central inflammation	ELISA, Simoa Metabolomic platforms (Olink, SomaScan)	Reflect neuroinflammation; correlate with Tau pathology and cognitive decline; track disease progression	Moderate to low specificity; assay variability; influenced by systemic conditions	[71,72]
Synaptic Markers Neurogranin, SNAP-25	Reflect synaptic integrity and dysfunction	ELISA, Simoa	Early indicators of synaptic loss; correlate with cognitive impairment	Limited plasma validation; variable assay sensitivity; less studied in blood	[89]
Oxidative Stress Markers 8-OHdG, Malondialdehyde, F2-isoprostanes	Indicators of oxidative DNA and lipid damage	ELISA, Mass Spectrometry	Reflect oxidative stress contributing to AD pathology; may indicate progression	Assay variability; low specificity; influenced by systemic oxidative stress	[83]
Metabolomic Markers Phosphatidyl-choline, Sphingomyelin	Reflect lipid metabolism and membrane integrity	Mass Spectrometry, Metabolomic platforms (Olink, SomaScan)	Altered lipid profiles in AD; potential early markers; improve diagnostic panels	High inter-individual variability; best used in multi-marker panels	[96]

This table summarizes key Alzheimer's disease biomarkers. Neuroinflammatory markers like YKL-40, sTREM2, and cytokines (IL-6, TNF-α, IL-1β) rise early and track progression but have moderate specificity and variability. Synaptic markers such as neurogranin and SNAP-25 reflect early synaptic loss, though plasma validation is limited. Oxidative stress markers (8-OHdG, MDA, F2-isoprostanes) indicate damage but lack disease specificity. Metabolomic markers, including changes in phosphatidylcholine and sphingomyelin, reflect lipid metabolism disruption and are best used in multi-analyte panels due to variability.

ANALYTICAL TECHNIQUES:

Technological advances in analytical platforms have made measuring ultra-low concentration Alzheimer's Disease (AD) biomarkers in peripheral blood plasma possible. Single Molecule Array (Simoa) digital immunoassay technology offers femtomolar sensitivity (10^{-15} M), effectively overcoming the severe blood dilution barrier that historically limited non-invasive biomarker detection.[97] This ultra-sensitive approach has been widely adopted for measuring plasma biomarkers, such as p-Tau isoforms, NFL, and GFAP. For example, Simoa assays for p-Tau217 have consistently demonstrated diagnostic accuracies exceeding 90% in distinguishing AD patients from controls across diverse cohorts, highlighting their robustness and reproducibility.[98] However, the high cost and requirement for specialized instrumentation may limit their accessibility in some clinical settings, particularly those with limited resources.

Lumipulse technology represents a significant advance, offering fully automated immunoassays for the measurement of key plasma biomarkers including p-Tau181, p-Tau217, and Aβ42/40.[34,50,51] Lumipulse assays (Fujirebio) represent fully automated Chemiluminescent Enzyme Immunoassays (CLEIA) designed specifically for high-throughput, routine clinical diagnostic laboratories. While single-molecule digital platforms like Simoa lead in ultra-high research sensitivity, Lumipulse bridges the critical gap between academic discovery and practical hospital-wide execution. [99]

Immunoprecipitation–Mass Spectrometry (IP-MS) is an analytical hybrid technique that couple's antibody-driven selective isolation with liquid chromatography–tandem mass spectrometry (LC-MS/MS) detection. While immunoassays rely on antibody binding intensity alone, IP-MS physically measures molecule mass-to-charge (m/z) ratios, providing high structural specificity for protein isoforms and post-translational modifications (PTMs).[100] This method is particularly valuable for measuring plasma Aβ42/40 ratios, with studies showing strong correlations between IP-MS results and amyloid PET imaging, as well as cerebrospinal fluid Aβ levels. Despite its analytical strengths, IP-MS demands specialized expertise and infrastructure, which may restrict its widespread adoption in routine clinical practice.[101]

Electrochemiluminescence immunoassays (ECLIA) offer multiplexed quantification of biomarkers, including total tau and Aβ isoforms.[102] Electrochemiluminescence Immunoassay (ECLIA) platforms—most prominently featured in platforms like Meso Scale Discovery (MSD) and Roche Elecsys—utilize electrochemical reactions to generate light signals. ECLIA balances the ultra-high research sensitivity of Simoa with automated laboratory throughput, making it a powerful platform for both multi-analyte research panels and clinical workflows.[100]

Recent progress in fully automated immunoassay analysers represents the final step in translating Alzheimer's Disease (AD) fluid biomarkers from academic research into widespread clinical practice. By automating the entire diagnostic workflow, these platforms eliminate manual handling errors, deliver high throughput, and ensure inter-laboratory standardization across routine hospital networks.[103] Automation is critical for scaling up screening efforts and longitudinal monitoring of AD in real-world settings, addressing the need for accessibility and reproducibility.

Collectively, these analytical technological innovations form an integrated diagnostic toolkit for Alzheimer's Disease (AD) fluid biomarkers. Rather than competing against one another, ultra-sensitive platforms (Simoa), automated clinical analyzers (Lumipulse, ECLIA), and gold-standard reference techniques (IP-MS) play complementary roles across a tiered global healthcare framework.[103] Blood-based biomarkers (BBMs) represent a major shift in Alzheimer's disease (AD) clinical care. Moving from invasive, high-cost diagnostics —such as cerebrospinal fluid (CSF) lumbar punctures and Amyloid/Tau PET imaging—to minimally invasive plasma assays dramatically lower the barrier to early detection.[104]

CONTEXT OF USE, CHALLENGES AND LIMITATIONS OF BLOOD BIOMARKERS:

Blood-based biomarkers (BBMs) represent a monumental paradigm shift in neurodegenerative medicine. By providing a scalable, non-invasive window into the living brain, they enable a transition from reactive late-stage symptom management to proactive early-stage intervention.[105,106]

This capacity for early detection signals a major shift in clinical practice. Integrating blood-based assays reduces reliance on Positron Emission Tomography imaging and lumbar punctures, bypassing high diagnostic costs and invasive procedures. Furthermore, the scalability of population-wide screening facilitates a restructured diagnostic workflow, enabling a more efficient allocation of resources across specialized neurodegenerative centres.[98]

summarizes current evidence on blood biomarker dynamics across the AD continuum and outlines both established and potential contexts of clinical application.

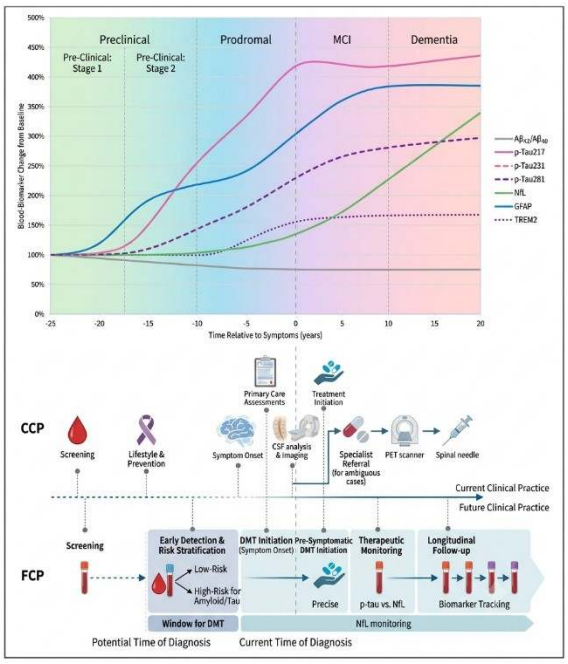

Figure 5: Temporal Trajectories and Potential Clinical Application Framework of Blood Biomarkers Across the Alzheimer's Disease Continuum.

Temporal trajectories of blood biomarkers across the Alzheimer's disease continuum, from the preclinical phase to dementia. Early changes precede symptom onset by many years, while subsequent increases reflect progression of pathology, neurodegeneration, and glial activation. The lower panel contrasts current reliance on CSF and imaging with future perspectives where blood biomarkers will support early detection, stratification, therapeutic monitoring and longitudinal follow-up.

While blood biomarkers offer unparalleled accessibility and potential for large-scale AD screening, transitioning them from controlled research settings into routine clinical practice presents significant challenges that demand critical appraisal. This evaluation focuses on three main areas: pre-analytical variability, clinical and comorbid confounding factors, and analytical and regulatory standardization. [107,108] The implementation of a two-cut-off approach is a sophisticated clinical triaging strategy that enhances the practical utility of AD blood tests. By intentionally creating an intermediate "Gray zone", this method addresses the inherent variability of current assays, balancing high diagnostic sensitivity (to rule out disease) with high specificity (to rule in disease).[109,110,111]

The implementation of a "Gray zone" or intermediate zone in AD blood biomarker testing necessitates the development of a specific, integrated care protocol tailored for individuals with indeterminate results. While this category advances our understanding of the AD spectrum, it also introduces significant ethical challenges and mandates systemic changes to ensure all patients receive adequate assistance and support.

Despite recent technological advancements and the development of high-throughput automated analysers, the widespread implementation of Alzheimer's Disease (AD) blood biomarkers into routine healthcare systems is fundamentally stalled. The primary barriers are substantial infrastructure requirements and high costs, which disproportionately impact resource-limited environments and further widen global disparities in dementia care.[103]

Longitudinal measurements of biomarkers like NFL and GFAP offer valuable insights into neurodegeneration and disease progression, but their prognostic utility is limited by inter-individual variability and the absence of standardized thresholds.[64] While these markers have advanced our understanding of AD heterogeneity and enabled more nuanced patient stratification, biological and technical variability

continue to challenge the reproducibility of subtyping efforts.

The regulatory landscape is rapidly evolving, as proven by the recent FDA clearance of Lumi pulse plasma pTau217/Aβ42 ratio. This ratio has shown reliability in predicting the presence of amyloid plaques in cognitively impaired patients referring to specialized Memory Centres. [112] The p-tau/Aβ ratio (e.g., p-tau217/ $A\beta_{42}$ or p-tau181/ $A\beta_{42}$) has emerged as one of the most clinically powerful fluid biomarker metrics in Alzheimer's Disease (AD) diagnostics. By combining both primary hallmarks of AD into a single mathematical construct, this ratio provides superior diagnostic accuracy compared to single "mono-pathology" biomarkers evaluated in isolation.

The continuous formulation and refinement of clinical practice guidelines by leading international bodies, such as the Alzheimer's Association, is the definitive bridge translating blood-based biomarkers (BBMs) from experimental tools into standard medical care. These guidelines establish evidence-based protocols that define appropriate use criteria (AUC)—specifically detailing *who* should undergo testing, *when* in the diagnostic timeline testing is warranted, and *how* results should direct clinical management.[107]

This regulatory progress, alongside rapid scientific innovation, stresses the importance of balancing enthusiasm for technological advances with rigorous validation and critical interpretation.[113]

Ultimately, blood-based biomarkers represent a powerful and evolving toolkit for advancing AD care and research, but their ethical and effective widespread use requires ongoing attention to issues of analytical rigor, population diversity, and clinical correlation.[93] Only by integrating technological innovation, robust validation, and equitable access can the full potential of blood biomarkers be realized in transforming the landscape of AD.[107,108] Variability in pre-analytical procedures represents one of the primary drivers of assay inconsistencies across laboratories and clinical trials. Because blood plasma is a complex, biologically dynamic matrix compared to cerebrospinal fluid (CSF), strict standardization of pre-analytical protocols is mandatory to guarantee reproducible biomarker quantification.[114] such as sample collection and processing, along with differences in assay calibration, reagents, and interpretation thresholds, undermines the comparability of biomarker measurements obtained from different studies and platforms.[115] Addressing inter-laboratory variability is the foundational prerequisite for transitioning blood-based biomarkers (BBMs) from academic research tools to universally trusted clinical diagnostics. Without assay harmonization, numerical values generated on one platform or in one health network cannot be directly compared to those from another, severely limiting multi-centre clinical trials, meta-analyses, and global diagnostic consensus.[75]

Another critical challenge revolves around population diversity and generalizability. The vast majority of existing biomarker research has been conducted in relatively homogeneous, well-characterized cohorts, often lacking adequate representation of diverse ethnic, racial, and socioeconomic groups.[93] Addressing the underrepresentation of ethnically and demographically diverse cohorts in biomarker validation trials is essential to ensure that blood-based biomarkers (BBMs) perform equitably in real-world clinical care. Because early discovery studies predominantly analysed homogeneous, non-Hispanic white cohorts, translating these diagnostic thresholds directly across broader populations presents significant challenges in generalizability and accuracy.[116,117] Validating blood-based biomarkers (BBMs) across multi-ethnic, socioeconomically diverse cohorts with realistic medical profiles is the ultimate requirement for achieving health equity in Alzheimer's Disease (AD) care. Without broad-scale validation, advanced diagnostics and precision therapeutics risk being restricted to privileged, highly selected patient subgroups.[118]

In addition to technical and scientific considerations, the deployment of blood biomarkers, particularly for early detection and screening of asymptomatic individuals, introduces complex ethical and practical considerations.[119] Disclosure of biomarker results indicating increased AD risk may cause psychological distress, anxiety, or stigma, particularly in the absence of widely effective preventive or curative treatments. [120] Moreover, there are potential implications for employment, and social discrimination, underscoring the

need for careful consideration of the societal impact of biomarker-based diagnostics.[119]

To address these ethical concerns, it is essential to develop clear guidelines along with counselling practices that ensure that individuals are fully informed about the potential benefits and risks of biomarker testing, empowered to make autonomous decisions regarding their healthcare, and protected from potential harms associated with biomarker disclosure.[120]

The clinical integration of blood-based biomarkers (BBMs) into existing medical centres requires an organizational transformation. Moving from standard symptomatic or neuroimaging-based pathways to blood-biomarker-driven protocols requires updating clinical practices, retraining healthcare personnel, reorganizing laboratory-to-clinic workflows, and establishing new referral channels.

DISCUSSION AND CONCLUSIONS:

Blood-based biomarkers (BBMs) represent a definitive paradigm shift in neurodegenerative care. By translating fluid diagnostics from invasive cerebrospinal fluid (CSF) draws and costly Amyloid/Tau PET imaging into standard venipuncture assays, BBMs dramatically lower the logistical barrier to early detection, risk stratification, and scalable clinical trial design.[121] A comprehensive, multi-modal biomarker strategy that merges plasma Aβ42/40, p-Tau isoforms, NFL, and GFAP has demonstrated remarkable diagnostic accuracy, compensating for the weaknesses of single biomarker measurements.[27]

However, these exciting advances in the field of blood-based biomarkers do face a challenging and complex translation into routine clinical practice.[118] Indeed, their widespread implementation necessitates continued efforts toward assay standardization, rigorous validation across diverse populations, regulatory approval, and establishment of ethical frameworks to ensure responsible and equitable use.[119] Translating global clinical guidelines into diverse real-world healthcare settings represents the final step in the clinical rollout of Alzheimer's Disease (AD) blood-based biomarkers (BBMs). Expert recommendations (such as those from the Alzheimer's Association) provide brand-agnostic performance benchmarks (e.g., ≥90%diagnostic accuracy). However, these guidelines must be adapted to fit local infrastructure, cultural attitudes toward cognitive health, and resource availability across different medical systems. Addressing these challenges will be critical to realizing the full potential of blood biomarkers in transforming AD care.

As novel anti-amyloid and other disease-modifying therapies continue to evolve[121], accessible and reliable blood biomarkers will become indispensable tools for identifying appropriate candidates for treatment, monitoring therapeutic efficacy in real time, and refining clinical decision-making to optimize patient outcomes.[122] To support this, international collaborations must prioritize harmonizing pre-analytical procedures, assay platforms, and interpretation criteria to ensure consistency and comparability across clinical and research settings.[114] Expanding research to include ethnically, racially, and socioeconomically diverse, community-based populations will enhance the generalizability of findings and promote equity in diagnosis and care. Ethical oversight frameworks addressing informed consent, risk communication, and data privacy are equally vital, particularly as biomarker testing moves toward earlier, pre-symptomatic diagnosis.[120] Finally, integrating blood biomarkers into comprehensive screening, diagnostic, and therapeutic algorithms across both specialist and primary care environments will be crucial for maximizing their clinical impact. The field has progressed rapidly, moving from conceptual research to tangible clinical application. Looking ahead, the integration of these biomarkers into multidimensional diagnostic models, combining clinical assessments, genetic information, cognitive testing, and lifestyle factors, will be critical.[123]

Key areas for future research include conducting longitudinal studies across ethnically and clinically diverse cohorts to capture the full spectrum of AD heterogeneity, developing multi-biomarker panels to enable disease subtyping and more accurate prognosis, validating biomarkers as surrogate endpoints in therapeutic trials, implementing blood biomarker testing in real-world primary care settings, and establishing robust ethical frameworks for biomarker disclosure and clinical decision-making.[122] Blood-based biomarkers promise to revolutionize Alzheimer's care by shifting

it from a late-stage model to a proactive and timely personalized approach. This transformation will enable the early identification of individuals at risk, guide targeted therapies tailored to individual disease biology, and facilitate continuous, minimally burdensome monitoring of disease progression, thereby improving outcomes for patients and alleviating strain on healthcare systems worldwide.

SEARCH STRATEGY:

For this narrative review on blood-based biomarkers in Alzheimer's disease, a comprehensive literature search was conducted to capture the most recent and relevant advances in the field. Databases, including PubMed, Scopus and Web of Science, were queried using a combination of

keywords and Mesh terms related to Alzheimer's disease, blood biomarkers and diagnostic technologies. The search prioritized original research articles, clinical trials, systematic reviews and meta-analyses published up to early 2025. Emphasis was placed on studies reporting biomarker discovery, validation, clinical applications and technological advancements. Selection criteria favoured studies that elucidate the biological relevance, diagnostic accuracy, and translational potential of blood biomarkers across the AD continuum. Articles addressing challenges, ethical considerations and future directions were also included to provide a holistic perspective. Reference lists of key publications were hand-searched to identify additional pertinent studies.

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