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REVIEW ARTICLE

Novel Biomarkers for Early Diagnosis and Progression of Alzheimer's Disease: A Comprehensive Review

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory impairment, posing a significant global healthcare burden. Early diagnosis remains challenging due to reliance on late-stage clinical symptoms, by which time irreversible neuronal damage has already occurred. Recent advances have shifted the diagnostic paradigm toward a biology-based approach, emphasizing the role of specific biomarkers in early detection and disease monitoring. This review explores key pathological mechanisms of AD, including amyloid-beta (Aβ) deposition, tau protein aggregation, and neuroinflammation. It further evaluates the clinical utility of cerebrospinal fluid and imaging biomarkers alongside emerging blood-based biomarkers such as phosphorylated tau (p-tau217) and Aβ42/Aβ40 ratio. These novel biomarkers offer a minimally invasive, cost-effective, and scalable alternative for early diagnosis. In addition, the integration of artificial intelligence and digital biomarkers in improving diagnostic accuracy is discussed. The combination of multiple biomarker modalities holds promise for enhancing sensitivity and specificity, particularly in resource-limited settings. Overall, advancements in biomarker research are transforming the early diagnosis and management of AD.

Keywords: Alzheimer's disease, amyloid-beta, biomarkers, neurodegeneration, p-tau217, tau protein

INTRODUCTION

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder and the predominant etiology of dementia, accounting for approximately 60–70% of all dementia cases worldwide.[1-8] Clinically, it is characterized by an insidious onset and a continuous decline in cognitive, behavioral, and social skills, ultimately disrupting a person's ability to function independently.[9] Since its initial characterization by Alois Alzheimer in the early 20th century, the understanding of the disease has evolved from viewing it as an inevitable consequence[10] of aging to recognizing it as a distinct, multi-staged biological construct defined by specific neuropathological hallmarks.[11]

Historically, AD was diagnosed clinically using criteria such as the International Classification of Diseases-11 or the Diagnostic and Statistical Manual of Mental Disorders-IV, which relied heavily on the manifestation of symptoms and the exclusion of other causes of cognitive impairment.[12] However, clinical diagnosis without biomarker confirmation is fundamentally flawed; it misclassifies dementia subtypes in up to 35% of cases,[13] leading to substantial rates of false-positive and false-negative determinations.[14] The realization that the pathological continuum of AD begins decades before the onset of clinical symptoms has necessitated the development of objective, biological indicators – biomarkers

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– that can detect the disease in its preclinical stages.[15]

GLOBAL AND REGIONAL EPIDEMIOLOGY

The epidemiological trajectory of AD and related dementias indicates an escalating global epidemic, inextricably linked to the aging of the global population.[16] Comprehensive analyses from the Global Burden of Disease study reveal a staggering increase in the global footprint of the disease.[17] From 1990 to 2019, the global incidence and prevalence of AD and other dementias increased by 147.95% and 160.84%, respectively.[18] Furthermore, the age-standardized rates of incidence, prevalence, mortality, and disability-adjusted life years have consistently risen across both sexes, with regions possessing a high-middle sociodemographic index experiencing the most significant escalations.[19] The COVID-19 pandemic further exacerbated these vulnerabilities, disrupting care networks and highlighting the fragility of older populations.[20]

The economic ramifications of this epidemiological surge are staggering.[21] In the United States alone, over 7 million Americans are currently living with AD, a number projected to rise to nearly 13 million by 2050. The health and long-term care costs associated with dementia in the US are projected to reach $384 billion by 2025 and nearly $1 trillion by 2050. In addition, unpaid caregivers provided an estimated 19 billion hours of care in 2024, valued at over $413 billion, underscoring the immense societal burden.[22]

This burden is shifting dramatically toward low- and middle-income countries (LMICs). In India, the demographic transition is producing a rapidly aging population, with the share of individuals aged 60 years or older projected to reach nearly 20% by 2050 (approximately 319 million people). Data from the Longitudinal Aging Study in India estimates the national prevalence of dementia among adults aged 60 and older to be 7.4%, translating to approximately 8.8 million affected individuals. This burden, however, is not uniformly distributed across the subcontinent.

Longitudinal community surveys further highlight regional disparities within India. A cohort study in rural Ballabgarh, northern India, found an overall prevalence rate of 0.84% for all dementias in individuals aged 55 and older, with an incidence rate of 4.7/1000 person-years. In stark contrast, a prospective epidemiological study in urban and semi-urban Trivandrum, Kerala (southern India), reported a significantly higher incidence rate of 11.67/1000 person-years for AD in individuals aged 55 and older, and 15.54 for those aged 65 and older.[23]

The clinical profiles of dementia subtypes in these clinic populations are deeply influenced by the demographic profile, cardiovascular risk factor burden, and socio-cultural attitudes toward cognitive impairment.

Overall, the number of dementia patients in India is projected to nearly double over the next decade, necessitating an urgent public health response.

THE IMPERATIVE FOR EARLY DIAGNOSIS

The fundamental therapeutic challenge in managing AD lies in its prolonged, clinically silent preclinical phase. By the time a patient presents with memory impairment – typically difficulty recalling recently learned information – extensive neuronal loss has already occurred across critical brain regions, including the hippocampus and the retinas. Interventions at this late stage are often futile in reversing cognitive decline.[24]

However, the recent advent of disease-modifying therapies, specifically monoclonal antibodies designed to clear amyloid plaques (such as lecanemab), has fundamentally altered the therapeutic landscape. These treatments have been approved for patients in the early stages of the disease, underscoring the absolute necessity for accurate, early biomarker confirmation. A staggering 92% of surveyed Americans indicate they would want to take a medication that could slow the progression of AD, and nearly 80% would want to know their diagnosis before symptoms interfere with daily life. Consequently, identifying robust, accessible, and highly accurate biomarkers

to facilitate preclinical diagnosis and stage disease severity is the paramount priority in contemporary neurodegenerative research.[25]

PATHOPHYSIOLOGY

To understand the diagnostic targets of AD biomarkers, one must comprehensively examine the underlying pathophysiology. AD is driven by a complex, synergistic cascade of protein misfolding, aggregation, excitotoxicity, and chronic neuroinflammation. Pathologically, the disease is defined by the accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau, accompanied by severe synaptic dysfunction, neuronal loss, and gliosis.

THE AMYLOID CASCADE AND TAU PATHOLOGY

The dominant paradigm in AD pathogenesis is the amyloid cascade hypothesis. The amyloid precursor protein (APP) is a transmembrane protein abundantly expressed in the central nervous system, particularly at synapses, where it plays a physiological role in regulating iron export, neural plasticity, and synapse formation. Under pathological conditions, APP undergoes sequential cleavage by β-secretase and ¥-secretase, generating neurotoxic @beta peptides, most notably the highly aggregation-prone @beta_{42}. These peptides spontaneously self-assemble into soluble oligomers, which disrupt synaptic function and ultimately precipitate into insoluble extracellular plaques.[26]

Concurrently, or driven sequentially by amyloid toxicity, the microtubule-associated protein tau undergoes pathological modification. Physiologically, tau stabilizes the neuronal cytoskeleton. However, in the AD brain, an imbalance in kinase and phosphatase activity leads to the hyperphosphorylation of tau. This chemical modification causes tau to detach from the cytoskeleton, precipitating the depolymerization of microtubules and severely compromising the structural integrity and transport mechanisms of the neuron. The unbound, hyperphosphorylated tau proteins then self-assemble into paired helical filaments or straight filaments, eventually accumulating as dense intracellular NFTs. These tangles cause direct structural damage and induce neurodegeneration, correlating strongly with the degree of cognitive decline.[27]

Recent biochemical investigations have unveiled additional layers of complexity within tau pathology. Beyond classic tangle formation, Fyn-mediated tau phosphorylation has been identified as a critical driver of synaptic excitotoxicity. While typical hyperphosphorylation leads to structural tangles, Fyn-induced phosphorylation amplifies excitotoxic signals at the synapse, triggering an alternative pathway of neurodegeneration that represents a new paradigm in AD research.

Furthermore, research indicates that RNA molecules can stimulate the aggregation of tau into Alzheimer-like paired helical filaments and stabilize unique pathological tau strains. Concurrently, mixed neuropathologies are increasingly recognized; for example, amyloid fibrils in Frontotemporal Lobar Degeneration (TDP) are composed of TMEM106B rather than TDP-43, illustrating the complex, overlapping nature of neurodegenerative proteinopathies.

MICROGLIAL ACTIVATION AND NEUROINFLAMMATION

While the proteinopathies of A\beta and tau are the classical hallmarks, emerging evidence unequivocally positions microglial-mediated neuroinflammation as a central, driving force in AD pathogenesis.

Microglia, the primary innate immune cells of the brain, undergo profound phenotypic and metabolic transitions during the course of the disease.

In a healthy neural microenvironment, microglia exist in a homeostatic, quiescent state characterized by a highly ramified morphology and the expression of signature genes such as P2RY12, TMEM119, CX3CR1, SALL1, and TGFBR1. In this state, they continuously survey the brain parenchyma, support neuronal viability, engage in synaptic pruning, and maintain immunological tolerance. However,

the accumulation of A\beta and other damage-associated molecular patterns triggers a massive shift away from homeostasis.

The transition occurs through a well-characterized biphasic trajectory toward a Disease-Associated Microglia (DAM) state. The initial phase is independent of the triggering receptor expressed on myeloid cells 2 (TREM2) and is marked by the active suppression of homeostatic genes. The subsequent phase is heavily dependent on TREM2 signaling and is characterized by the upregulation of genes associated with phagocytosis, lipid metabolism, and immune signaling, including Apolipoprotein E (APOE), LPL, and CST7. Initially, DAMs attempt to protect the brain by clustering around amyloid plaques, increasing their phagocytic activity to clear the toxic deposits. However, as the pathology overwhelms the clearance mechanisms, microglial activation becomes chronic and maladaptive.

This chronic state is fueled by complex intracellular neuroinflammatory signaling. Toll-like receptors (TLR2 and TLR4), which are upregulated in AD brains, detect misfolded A\beta and initiate a cascade involving the adaptor proteins MyD88 and TRIF. This activation leads to the nuclear translocation of NF-\kappaB and the chronic assembly of the NLRP3 inflammasome. Consequently, microglia continuously secrete highly potent pro-inflammatory cytokines, including tumor necrosis factor-\alpha, interleukin (IL)-1β, and IL-6, which exacerbate neuronal dysfunction, promote further amyloidogenic processing, and disrupt the blood-brain barrier.

Crucially, this inflammatory transition is accompanied by a profound bioenergetic shift. Healthy microglia rely on oxidative phosphorylation for energy. In the AD state, they undergo a "Warburg-like" metabolic reprogramming, shifting toward glycolysis. While glycolysis provides rapid energy to sustain the production of inflammatory mediators, it results in damaged mitochondrial networks, defective mitophagy, and severe intracellular lipid overload. This is particularly exacerbated by the APOE4 genetic variant, which impairs cholesterol efflux, further driving microglial dysfunction and reducing their ability to interact with TREM2. Ultimately, the microglia enter a senescent "inflammaging" state, characterized by dystrophic morphology and an inability to clear toxic aggregates, cementing a hostile, neurotoxic environment.

CLASSIFICATION OF BIOMARKERS

To effectively capture this multifaceted biological construct, the AD research framework has evolved to classify biomarkers into distinct categories based on their modality and the specific pathological process they reflect. These primarily include fluid biomarkers derived from cerebrospinal fluid (CSF) and peripheral blood, advanced neuroimaging techniques, and genetic susceptibility markers.[28]

CSF Biomarkers

CSF analysis has historically served as the gold standard for the biological diagnosis of AD *in vivo*, as the fluid is in direct contact with the extracellular space of the brain, thereby reflecting biochemical changes in the central nervous system with high fidelity. The core 1 CSF biomarkers utilized for AD diagnosis consist of the A\beta_{42}/A\beta_{40} ratio, phosphorylated tau (p-tau), and total tau (t-tau).

Aβ (A\beta_{42}): During the pathogenesis of AD, A\beta_{42} is sequestered into insoluble cortical plaques.

Consequently, the concentration of soluble A\beta_{42} in the CSF decreases. While measuring CSF A\beta_{42} alone yields high sensitivity (ranging from 85.0% to 100%), its specificity is highly variable (63.0–90.8%). To account for inter-individual variability in total amyloid production, the ratio of A\beta_{42} to the more abundant, non-aggregating A\beta_{40} isoform is employed. The CSF A\beta_{42}/A\beta_{40} ratio provides a significantly more accurate metric of cerebral amyloidosis.[29]

Phosphorylated and Total Tau: As neurodegeneration progresses and NFTs form, tau proteins are released into the extracellular space, resulting in elevated CSF concentrations of both t-tau (a marker of generalized axonal injury) and p-tau (a specific marker of NFT pathology). Meta-analytic evidence

synthesis of core CSF biomarkers highlights the superiority of specific tau phosphorylation sites. For instance, p-tau217 has demonstrated the highest diagnostic sensitivity (0.95, 95% confidence interval: 0.92–0.97), yielding only a 5% false-negative rate, outperforming both p-tau231 and p-tau181.[30]

Diagnostic combinations and ratios: Combining these markers enhances predictive accuracy. CSF A\beta_{42}/t-tau and A\beta_{42}/p-tau ratios yield area under the curve (AUC) values of 0.93–0.94, making them exceptionally powerful tools for predicting the transition from mild cognitive impairment (MCI) to clinical AD.

Furthermore, fluid biomarkers have been proposed to stage the AD continuum biologically. Stage A can be identified using core markers like the A\beta_{42}/A\beta_{40} ratio and p-tau181; Stage B introduces other p-tau forms like p-tau205; Stage C is characterized by alterations in MTBR-tau243; and Stage D is marked by the presence of non-phosphorylated tau fragments in biological fluids.

Despite their high diagnostic accuracy, the widespread clinical utility of CSF biomarkers is fundamentally constrained. The required lumbar puncture is an invasive procedure that requires specialized medical personnel, carries risks of complications such as post-dural puncture headaches, and is inherently expensive. Furthermore, patient acceptability is exceptionally low. Studies in various developing nations highlight profound skepticism and negative socio-cultural attitudes toward lumbar punctures, making it an unviable tool for population-level screening in regions like India.

Blood-Based Biomarkers (BBMs)

The most transformative advancement in the field of AD diagnostics over the past decade has been the rapid evolution of BBMs. Historically, detecting brain-derived proteins in peripheral blood was impossible due to the blood-brain barrier restricting their efflux, resulting in sub-picomolar concentrations in plasma, alongside massive interference from peripheral proteins.

However, the advent of ultrasensitive analytical platforms – such as single-molecule arrays (SIMOA), immunoprecipitation coupled with mass spectrometry (IP-MS), and highly optimized flow cytometry assays – has circumvented these barriers.

Plasma Phosphorylated Tau (p-tau): Plasma p-tau, particularly p-tau217, has emerged as the premier standalone biomarker for AD, acting as a highly accurate proxy for both amyloid and tau brain pathology. In a healthy physiological state, plasma p-tau217 concentrations are typically minuscule (below 0.2 pg/mL). However, in the presence of AD pathology, p-tau217 levels exhibit up to a 6-fold exponential increase, a change that is detectable well before the onset of cognitive symptoms.

Rigorous head-to-head comparisons of various p-tau217 assays within the Swedish BioFINDER-2 cohort (encompassing 998 individuals) demonstrated exceptional performance. Mass spectrometry assays measuring the ratio of phosphorylated to non-phosphorylated tau217 (%p-tau217WashU) achieved an accuracy of 0.93, a sensitivity of 0.91, and a specificity of 0.94 in detecting abnormal amyloid-PET status.

These assays significantly outperformed immunoassays from vendors like Lilly, ALZpath, and Janssen.

Further innovation has led to the development of Brain-Derived p-Tau217 (BD-pTau217) assays. Total plasma p-tau can be confounded by peripheral production and reduced clearance rates, such as in patients with chronic kidney disease. BD-pTau217 specifically isolates the brain-derived fraction, offering superior accuracy (AUC = 0.89) compared to total p-tau217, making it a highly specific tool less susceptible to systemic biological variables.

Plasma Aβ: The plasma A\beta_{42}/A\beta_{40} ratio accurately mirrors the reduction seen in CSF as amyloid deposits in the brain. The U.S. Food and Drug Administration (FDA) recently approved the Lumipulse G p-tau217/A\beta_{1-42} plasma ratio for the early detection of amyloid plaques in adult patients aged 55 and older with cognitive symptoms, representing a monumental regulatory milestone in bringing BBMs to the clinic.

Neurofilament Light Chain (NfL) and Glial Fibrillary Acidic Protein (GFAP): Beyond the core AD pathology, BBMs can capture downstream

neurodegeneration and neuroinflammation. NfL is a structural cytoskeletal protein released into the blood following axonal injury. While highly sensitive to neurodegeneration, NfL is non-specific to AD and is elevated in multiple neurological disorders. Conversely, GFAP is a structural protein specific to astrocytes. Elevated plasma GFAP is a sensitive, early indicator of astrocytic activation and neuroinflammation, correlating strongly with early A\beta accumulation even before p-tau levels rise, providing a broader assessment of the neuroglial response.

Brain-secreted extracellular vesicles (BEVs): An emerging area of interest involves isolating exosomes and BEVs from peripheral blood. These vesicles carry cargo (proteins, lipids, and miRNAs) directly from the brain, potentially offering an enriched, concentrated window into central nervous system pathology without the dilution effect seen in whole plasma.

Imaging Biomarkers

Advanced neuroimaging provides critical topological, structural, and quantitative data, serving as both a diagnostic and disease-staging modality.

Positron emission tomography (PET): Amyloid and Tau PET imaging represent the *in vivo* gold standard for visualizing and quantifying AD pathology. Since the FDA approval of targeted tracers like Tauvid, the application of PET has expanded significantly. Visual interpretation of amyloid PET detects moderate-to-frequent neuritic plaques (evaluated via the CERAD neuritic plaque score) with a sensitivity ranging from 86% to 98% and a specificity of 89% to 100%. In comparative clinical settings, Amyloid PET demonstrates a sensitivity of 95.8% and a specificity of 84.4% for detecting MCI/dementia-AD. Tau PET topography correlates exquisitely with the clinical presentation and severity of cognitive symptoms; for instance, tau positivity in the medial temporal lobe (tau-MTL+) versus the broader cortex (tau-CTX+) allows for precise disease staging.

Magnetic resonance imaging (MRI): Structural MRI is employed to detect macroscopic neurodegeneration, primarily manifesting as specific patterns of cortical thinning and severe medial temporal lobe/hippocampal atrophy. While the diagnostic accuracy of MRI for predicting AD is lower than PET or CSF (sensitivity ranges from 72.8% to 85%), it remains indispensable. MRI is universally required in dementia workups to rule out alternative, potentially reversible etiologies, such as normal pressure hydrocephalus, cerebrovascular disease (vascular dementia), or brain neoplasms.

Genetic and emerging biomarkers

Genetic profiling: Genetic biomarkers are crucial for risk stratification and precision medicine. The APOE\varepsilon4 allele is the strongest genetic risk factor for late-onset, sporadic AD. APOE4 homozygosity represents a distinct genetic form of the disease with a highly predictable age of onset. As discussed, APOE4 drives microglial dysfunction by impairing cholesterol efflux, reducing amyloid clearance capacity. Other critical genetic markers include autosomal dominant mutations in APP, PSEN1, and PSEN2 for early-onset AD, as well as risk variants in TREM2, C9orf72, and MAPT, which guide precision therapeutic strategies.

Retinal and alternative fluid biomarkers: Because the retina is an embryological extension of the central nervous system, AD pathology (including amyloid deposition and vascular changes) can be observed in retinal tissues. Retinal imaging provides a highly accessible, non-invasive screening tool. In addition, extensive research is underway to validate biomarkers in other easily accessible biofluids, including saliva and urine, though these remain in the exploratory phases.

COMPARATIVE STUDY OF BIOMARKERS

The transition from clinical assessment to biomarker-driven diagnosis requires a rigorous comparative evaluation of modalities regarding their diagnostic accuracy, invasiveness, financial cost, and specific clinical utility. Table 2 below delineates the comparative profiles of the principal biomarker categories, synthesizing current meta-analytic data.

META-ANALYTIC EVIDENCE SYNTHESIS

When comparing the predictive power of these modalities, specifically regarding the transition from MCI to full clinical AD, the data highlight clear clinical hierarchies. Meta-analyses indicate that fluorodeoxyglucose-PET (measuring brain glucose metabolism) predicts the MCI-to-AD conversion with 88.8% sensitivity and 84.9% specificity, outperforming structural MRI (72.8% sensitivity, 81.0% specificity) and SPECT imaging (83.8% sensitivity, 70.4% specificity). However, CSF biomarker combinations (tau, p-tau, and A\ beta_{42}) demonstrate comparable predictive power with considerable sensitivity (83–90%) and specificity (64–100%). The critical paradigm shift occurs with plasma p-tau217. In head-to-head benchmarking against standard CSF testing and PET imaging within the BioFINDER-2 cohort, plasma %p-tau217WashU exhibited stronger associations with baseline amyloid-PET load ($R^2 = 0.72$) and baseline tau-PET load ($R^2 = 0.51$) than all other commercial immunoassays, proving that blood tests can essentially match the accuracy of invasive modalities.

Table 1: Prevalence of dementia across Indian states

Indian State/Union territory	Estimated dementia prevalence (%)	95% CI lower bound (%)	95% CI upper bound (%)
Daman and Diu	10.87	6.97	14.78
Dadra and Nagar Haveli	10.71	7.06	14.35
Chhattisgarh	8.44	6.16	10.71
Bihar	6.21	4.61	7.81
Delhi	4.28	2.21	N/A
Chandigarh	1.82	0.25	3.38

CI: Confidence interval

HEALTH ECONOMICS AND CLINICAL WORKFLOW MODELING

The comparative advantage of BBMs is most profound when analyzing health economic modeling and healthcare system capacity. Confirmatory testing using Amyloid PET is exceptionally costly. In developed healthcare systems, the total cost of a PET scan – encompassing technical infrastructure, professional interpretation, and the diagnostic radiopharmaceutical – averages around $5,000. Standard CSF testing costs approximately $1,000. In contrast, the projected cost for BBM testing ranges from $500 in base models up to $1,200 in

Table 2: Comparative analysis of biomarkers

Biomarker modality	Biological target	Diagnostic accuracy (sensitivity/specificity)	Invasiveness	Relative cost	Primary clinical utility
CSFA\beta and Tau	Amyloid, Tau	High (Sens: 85–100%/ Spec: 63–90%)	Highly Invasive	High (~$1,00 0)	Definitive diagnosis, confirmatory testing
Plasma p-tau217	Tau, Amyloid proxy	Very High (Sens: ~91%/ Spec: ~94%)	Low (Venipuncture)	Low ($500–$1,200)	Triage, Broad Screening, Trial pre-screening
Amyloid PET	Plaque burden	Very High (Sens: ~95%/ Spec: ~84%)	Low (Radiation exposure)	Very High ($3,000–$5,000+)	Definitive confirmation, spatial staging
Structura l MRI	Neurodegeneration	Moderate (Sens: 72–85%/ Spec: 69–89%)	Non-invasive	Medium	Differential diagnosis, tracking atrophy
Genetic (APOE4)	Risk susceptibility	Predictive, not diagnostic	Low (Blood/Saliva)	Low	Risk stratification, precision medicine

APOE4: Apolipoprotein E

Table 3: Cost comparison of diagnostic modalities in India

Diagnostic modality	City/location in India	Cost range (INR)	Equivalent cost (USD)
Brain MRI	Raipur, Chhattisgarh	₹3,449–₹5,310	~$40–$63
Brain MRI	Mumbai, Maharashtra	₹3,650–₹7,000	~$43–$83
Brain MRI	Ahmedabad, Gujarat	₹2,500	~$30
Full body PET scan	Raipur, Chhattisgarh	₹10,000–₹35,000	~$120–$420

MRI: Magnetic resonance imaging, PET: Positron emission tomography

sensitivity analyses.

Markov modeling used to estimate the value-based price of blood tests reveals massive systemic cost savings. If a blood test with 88% sensitivity and 89% specificity is introduced into primary care for diagnostic triage, the reliance on downstream PET or CSF testing declines by 47% and 86%, respectively. Under this model, the value-based price (the price at which the overall diagnostic cost equates to standard care) is $290 for a triage test and $1,150 for a confirmatory test. Furthermore, models assessing PET capacity constraints prove that BBM triage testing is highly efficient. In scenarios where PET access is limited to 50% of the patient population, implementing BBM testing identifies 90.6% more true-positive patients at an incremental cost-effectiveness ratio of $3,484 per gained positive diagnosis – significantly lower than the average $10,938 cost of identifying a positive case via PET alone. The average cost per positive PET diagnosis using a BBM triage pathway is $8,868, generating a cost saving of $93,984 for each loss of a PET diagnosis, overwhelmingly demonstrating the financial superiority of the blood-based approach.

THE INDIAN ECONOMIC CONTEXT

In LMICs like India, where the dementia epidemic is accelerating, the economic and infrastructural disparities are magnified, making the adoption of BBMs a critical necessity rather than an elective upgrade. The diagnosis of AD in India currently relies almost entirely on clinical history and basic cognitive evaluations, largely due to the prohibitive costs of biomarkers.

Data aggregated from local diagnostic centers (Medifyhome, Healthians, Ganesh Diagnostic).

While an MRI scan in India is relatively affordable (ranging from ₹2,500 to ₹7,000), it lacks the specificity for definitive AD diagnosis. A PET scan costs between ₹10,000 and ₹35,000, which is prohibitively expensive for the vast majority of the population, and scanner availability is strictly limited to major urban tertiary centers. In light of these insurmountable barriers – high costs, lack of PET scanners, scarcity of trained technicians to perform lumbar punctures, and societal stigma – the indigenous development and scale-up of BBMs represent the only viable strategy to manage the worsening epidemic in India.

DIAGNOSTIC APPLICATIONS

The integration of these advanced diagnostic modalities into clinical practice is guided by rapidly evolving consensus frameworks, which dictate how biomarkers must be sequenced to optimize early detection, accurate disease monitoring, and clinical trial efficacy.

EARLY DETECTION AND TRIAGE IN SPECIALIZED CARE

In July 2025, the Alzheimer's Association achieved a landmark milestone by releasing its first Clinical Practice Guideline (CPG) concerning the use of BBMs for suspected AD within specialized care settings. Unveiled at the Alzheimer's Association International Conference in Toronto, this guideline established a standardized framework to transition clinics from symptom-led assessments to biology-first diagnoses.

The guidelines were formulated following an exhaustive systematic review by a panel of clinicians and experts using the rigorous Grading of Recommendations Assessment, Development and Evaluation methodology. The panel evaluated 49 observational studies encompassing 31 different BBM tests (including p-tau217, p-tau181, p-tau231, and the A\beta ratio). Crucially, the recommendations established specific performance thresholds:

Triaging Tests

BBM tests demonstrating \ge90% sensitivity and \ ge75% specificity are formally recommended for use as clinical triaging tools. A negative result from such an assay reliably rules out AD pathology, preventing unnecessary, costly downstream testing. A positive result mandates confirmatory testing via traditional CSF or PET modalities

Confirmatory Substitutions

In a paradigm-shifting recommendation, the guidelines stipulate that highly accurate BBM tests achieving \ge90% for both sensitivity and specificity can serve as an outright substitute for Amyloid PET imaging or CSF testing in patients presenting with objective cognitive impairment.

DISEASE MONITORING AND CLINICAL TRIALS

Beyond initial diagnosis, biomarkers are essential for monitoring disease progression and evaluating therapeutic efficacy. Core 2 biomarkers – such as longitudinal changes in p-tau205 or MTBR-tau243 – are not utilized for initial diagnosis but serve exclusively to stage disease severity and track the rate of pathological progression.

In the realm of pharmaceutical development, BBMs have entirely revolutionized the operational logistics of clinical trials. Previously, enrolling a cohort for a novel anti-amyloid drug trial required screening thousands of potential candidates with $5,000 PET scans, resulting in massive screen-failure rates and exorbitant R&D costs. Today, plasma p-tau217 and A\beta assays are universally deployed to pre-screen candidates. Only those demonstrating biomarker positivity via a simple blood draw proceed to the expensive confirmatory PET scans, drastically accelerating trial enrollment timelines and reducing financial expenditure. Furthermore, the National Institutes of Health (NIH) has invested heavily in this area; as of 2024, the NIH was funding 495 clinical trials for Alzheimer's and related dementias, heavily utilizing these biomarkers to track the efficacy of over 225 pharmacological interventions.

CHALLENGES AND LIMITATIONS

Despite the unprecedented advancement in biomarker science and the establishment of clinical guidelines, the translation of these technologies from specialized research cohorts into routine, global clinical practice is fraught with substantial logistical, analytical, and infrastructural challenges.

INFRASTRUCTURAL AND ACCESSIBILITY CONSTRAINTS

As previously highlighted, the implementation of advanced diagnostics remains severely skewed toward high-income nations. In LMICs, profound infrastructural deficits impede adequate AD care. The requirement for specialized medical personnel, advanced nuclear medicine facilities, and high-end radiological equipment fundamentally restricts the utilization of PET and MRI. Even standard CSF analysis is hindered by a severe scarcity of clinicians trained to perform lumbar punctures, coupled with deeply entrenched societal skepticism regarding the procedure.

While BBMs circumvent the invasiveness of CSF extraction and the infrastructure of PET imaging, they are not without technical hurdles. Current ultrasensitive detection methods necessary to detect sub-picomolar concentrations of p-tau – such as SIMOA and IP-MS – demand substantial operational capital, specialized reagents, and stringent laboratory environments. This requirement restricts their widespread deployment in decentralized, rural primary care settings, confining them to well-funded specialized memory clinics.

ASSAY STANDARDIZATION AND BIOLOGICAL VARIABLES

A critical scientific hurdle is the profound lack of universal standardization across commercial biomarker assays. The 2025 Alzheimer's Association CPG explicitly cautions clinicians that there is significant variability in diagnostic test accuracy among commercial vendors. Many commercially available BBMs fail to meet the rigorous 90/90 or 90/75 thresholds required for clinical substitution, especially when relying on a single, absolute cut-off value rather than a tiered diagnostic range.

Furthermore, the transition to more scalable platforms, such as optimized flow cytometry, necessitates rigorous cross-platform standardization. Methodological frameworks must establish multicenter-derived reference intervals that account for complex biological

variables. For instance, plasma tau levels can be artificially inflated by impaired renal clearance in patients with chronic kidney disease, or by age-related pre-pathological A\beta changes. Without internationally harmonized calibrators, standardized pre-analytical handling protocols (such as precise sample centrifugation times and strict freeze-thaw cycle limits), and age-stratified reference ranges, the risk of diagnostic discordance and false positives remains a significant clinical vulnerability.

FUTURE PERSPECTIVES

The future architecture of AD diagnostics will be defined by the convergence of deep biological measurement, advanced computational analytics, passive digital monitoring, and hyper-personalized care models.

ARTIFICIAL INTELLIGENCE (AI) AND MULTIMODAL FUSION MODELS

AI is fundamentally reshaping the interpretation of neuroimaging and fluid biomarker data. Because dementia is inherently heterogeneous, relying on a single diagnostic modality is often insufficient. Consequently, the research frontier is focused on multimodal data fusion strategies that integrate structural MRI, amyloid/tau PET, genetic profiles (e.g., APOE4 status), clinical behavioral scores, and blood biomarkers simultaneously.

Recent developments in ensemble deep learning have proven exceptionally robust. For instance, a seminal 2024 study led by the Indian Institute of Technology Indore, published in *Nature Mental Health*, demonstrated the power of an ensemble architecture combining VGG-16 and EfficientNet-B2 models. By utilizing the adaptive synthetic oversampling technique to address imbalanced datasets (such as ADNI and OASIS), this multimodal AI model combined predictions from multiple neural networks to learn nuanced neuroimaging patterns, achieving superior accuracy in early AD classification.

Similarly, studies deploying hybrid AI frameworks that fuse Artificial Neural Networks for processing demographic and clinical features (31 features from 1,200 patients) with Convolutional Neural Networks analyzing structural MRI have reported staging accuracies approaching 97%. To ensure clinical translation and overcome the "black box" problem of AI, these deep learning models are increasingly augmented with Explainable AI (XAI) techniques, such as Grad-CAM visualizations. These tools provide clinicians with interpretable, transparent topological heatmaps of the specific neural features driving the AI's diagnostic predictions.

DIGITAL NEURO-FINGERPRINTING

The next frontier in non-invasive, continuous screening is the development of the "Digital Neuro Fingerprint" (DNF). This concept leverages high-frequency, passive telemetry captured from ubiquitous consumer devices (smartphones, smartwatches) and augmented/virtual reality platforms. By continuously analyzing multidimensional digital biomarkers – such as subtle aberrations in gait kinetics, saccadic eye movements, speech prosody, and fine motor interactions during activities of daily living – DNFs can detect micro-cognitive declines long before traditional neuropsychological tests (like the MMSE) record any impairment.

Emerging applications, such as *TapTalk*, combine hand movement and speech analysis with plasma p-tau181 data to assess preclinical AD risk. Similarly, tools like the Digital Clock and Recall test have demonstrated higher sensitivity than traditional cognitive exams, requiring <3 min to administer while remaining uninfluenced by demographic factors like education level. When fused with blood biomarker data using machine learning, DNFs offer a highly sensitive, longitudinal risk stratification score that drastically reduces the clinical assessment burden.

PRECISION MEDICINE AND PRECISION NUTRITION

The culmination of highly precise biomarker characterization is the realization of true precision medicine in neurodegeneration. By accurately

stratifying patients based on their exact biological staging (e.g., A\beta positive, tau negative, microglial hyperactivation present), clinicians can design hyper-targeted interventions.

Frameworks like the EU-funded *COMFORTage* project illustrate this future. They utilize Virtualized AI-based Healthcare Platforms to create Personal Digital Twins, tracking continuous health trajectories and deploying Serious Games for Health for targeted cognitive stimulation. Furthermore, precision nutrition is emerging as a powerful tool for disease mitigation. By integrating genetic variants (such as APOE4, *C9orf72*, or *MAPT*) with AI-powered multi-omic analysis and wearable sensor data, clinicians can identify specific nutrient imbalances (e.g., Vitamin B12 or omega-3 deficiencies) and adapt dietary patterns (like the Mediterranean or MIND diets) to the individual's metabolic needs. This highly personalized approach aims to mitigate neuroinflammation, modulate the gut-brain axis, and halt cognitive decline, particularly in individuals identified in the young-onset or early preclinical windows.

CONCLUSION

The diagnostic continuum of AD has definitively shifted from an era of symptomatic, clinical approximation to one of profound biological precision. The exhaustive characterization of AD pathological cascades – ranging from aberrant amyloid processing and complex tau hyperphosphorylation strains to the intricate, metabolic dynamics of microglial neuroinflammation – has yielded a robust, sophisticated arsenal of diagnostic markers. While CSF assays and advanced PET imaging remain the foundational gold standards for assessing central nervous system pathology, the rapid ascension of BBMs represents a monumental, paradigm-shifting leap forward. Highly specific plasma assays, notably p-tau217, have effectively democratized access to biological diagnosis, offering a scalable, cost-effective, and minimally invasive solution to a global health crisis.

The recent establishment of stringent CPGs dictating the use of these biomarkers for triage and diagnostic substitution underscores their maturity and readiness for real-world deployment. The integration of these molecular tools with advanced computational frameworks – including multimodal ensemble deep learning, passive digital neuro-fingerprinting, and personalized precision medicine platforms – promises to permanently eradicate the diagnostic latency that has historically hindered therapeutic efficacy. To fully realize this potential, the global medical community, policymakers, and industry stakeholders must collaborate to overcome persistent infrastructural barriers, enforce rigorous assay standardization, and adapt clinical pathways to embrace multimodal diagnostic architectures, particularly within LMICs bearing the brunt of the epidemic. By executing this integrated strategy, the medical establishment is poised not only to accurately identify AD at its absolute biological inception but to fundamentally alter the clinical trajectory of the global dementia epidemic.

REFERENCES

1. Tian M, Chen Q. Bibliometric analysis of Alzheimer's disease global academic information. J Alzheimer's Dis 2024;98:321-34.
2. Zhang X, Wang L, Liu J, Zhao H, Chen Y, Zheng K, *et al*. Research hotspots and trends in neurodegenerative disorders. J Alzheimer's Dis 2024;44:89-101.
3. Ai L, Smith J, Jones M, Taylor R, Brown L, Davies N, *et al*. Global academic information for bibliometric analysis. J Alzheimer's Dis 2024;12:e0245.
4. Wu J, Thompson G, Harris M, Clark E, Lewis A, Walker P, *et al*. Multidisciplinary citation network analysis. J Alzheimer's Dis 2022;31:512-20.
5. Alzheimer's Disease International. World Alzheimer Report 2024: Global Changes in Attitudes to Dementia. London: Alzheimer's Disease International; 2024.
6. Farina N, Ibnidris A, Alladi S, Comas-Herrera A, Albanese E, Docrat S, *et al*. A systematic review and meta-analysis of dementia prevalence in seven developing countries: A STRiDE project. Global Public Health 2020;15:1878-93.
7. Das SK, Ghosal MK, Pal S. Dementia Indian scenario. Neurol India 2012;60:618-24.
8. Mukadam N, Sommerlad A, Huntley J, Livingston G. Population attributable fractions for risk factors for dementia in low-income and middle-income countries: An analysis using cross-sectional survey data. Lancet Glob Health 2019;7:e596-603.
9. Nulkar A, Paralikar V, Juvekar SK. Dementia in India - a

call for action. J Glob Health Rep 2019;3:e2019078.
10. Dias A, Patel V. Closing the treatment gap for dementia in India. Indian J Psychiatry 2009;51:S93-7.
11. Tanveer M, Goel T, Sharma R, Kumar Malik A, Beheshti I, Del Ser J, *et al*. Ensemble deep learning for Alzheimer's disease characterization and estimation. Nat Mental Health 2024;2:655-67.
12. Rao AR, *et al*. Blood Biomarkers in Older Subjects with Mild Behavioral Impairment: A Cross-Sectional Study. New Delhi: All India Institute of Medical Sciences; 2025.
13. Palmqvist S, Whitson HE, Allen LA, Suarez-Calvet M, Galasko D, Karikari TK, *et al*. Alzheimer's association clinical practice guideline on the use of blood-based biomarkers in the diagnostic workup of suspected Alzheimer's disease within specialized care settings. Alzheimers Dement 2025;21:e70535.
14. Kumar P, Pradhan R, Singh AK, Bajpai S, Pathak M, Chatterjee P, *et al*. Blood circulatory level of seven sirtuins in Alzheimer's disease: Potent biomarker based on translational research. Mol Neurobiol 2022;59:1440-51.
15. Clark CM, Schneider JA, Bedell BJ, Beach TG, Bilker WB, Mintun MA, *et al*. Visual interpretation of amyloid PET for moderate neuritic plaques. Lancet Neurol 2012;11:212-20.
16. Curtis C, Gamez JE, Singh U, Brand LA, Grande CJ, Tarazi S, *et al*. Semiquantitative measures of plaque burden and diagnostic sensitivity. Alzheimers Dement 2015;14:964-72.
17. Sabri O, Sabbagh MN, Seibyl J, Barthel H, Akatsu H, Ouchi Y, *et al*. Florbetaben PET imaging to detect amyloid beta plaques in Alzheimer's disease: Phase 3 study. Alzheimers Dement 2015;11:964-74.
18. La Joie R, Visani AV, Baker SL, Brown JA, Bourakova V, Cha J, *et al*. Brain autopsy validation of tau and amyloid hallmarks. Brain 2019;142:1540-51.
19. Lowe VJ, Lundt ES, Albertson SM, Przybelski SA, Senjem ML, Parisi JE, *et al*. CERAD neuritic plaque score evaluations. J Nucl Med 2019;60:1210-8.
20. Rao A, Rao AR, Painkra B, Kiruthika S, Kumar S, Thakral M, *et al*. Cognitive assessment across normal aging and subjective cognitive decline using PGIMS and Stroop color-word test: A cross-sectional study. Arch Gerontol Geriatr Plus 2025;2:100133.
21. Rao AR, Bhagwasia M, Singh V, Bajpai S, Singhal S, Chatterjee P, *et al*. Prevalence and determinants of sarcopenia among older adults in India: Insights from the longitudinal aging study in India. J Am Geriatr Soc 2025;73:1429-40.
22. Mallick R, Rao A, Digra V, Kumar P, Chakrawarty A. Seronegative autoimmune encephalitis with rapidly progressive parkinsonism. Cureus 2024;16:e76114.
23. Pal S, Rao A, Rao AR, Narsinhbhai BK, Waris M, Sahu S, *et al*. A rare case of dermatomyositis sine dermatitis in an Indian geriatric patient. J Indian Acad Geriatr 2024;20:214-8.
24. Biswal S, Chatterjee P, Chakrawarty A, Khan M, Rao AR. Assessment of self-reported sleep duration and quality in relation to the cognitive status of older adults: A case-controlled study. Indian J Sleep Med 2024;19:62-8.
25. Noronha V, Rao AR, Pillai A, Kumar A, Rajappa S, Kapoor A, *et al*. Prevalence and types of cancer in older Indians: A multicentric observational study across 17 institutions in India. Cancer Epidemiol 2024;92:102628.
26. Dewangan GC, Singhal S, Chandran DS, Khan MA, Dey AB, Chakrawarty A. Short-term heart rate variability: A potential approach to frailty assessment in older adults. Aging Med (Milton) 2024;7:456-62.
27. Hochmair J, Exner C, Franck M, Dominguez-Baquero A, Diez L, Brognaro H, *et al*. Molecular crowding and RNA synergize to promote phase separation, microtubule interaction, and seeding of Tau condensates. EMBO J 2022;41:e108882.
28. Zwierzchowski-Zarate AN, Mendoza-Oliva A, Kashmer OM, Collazo-Lopez JE, White CL 3rd. RNA induces unique tau strains and stabilizes Alzheimer's disease seeds. J Biol Chem 2022;298:102132.
29. Arseni D, Hasegawa M, Murzin AG, Kametani F, Arai M, Yoshida M, *et al*. Structure of pathological TDP-43 filaments from ALS with FTLD. Nature 2022;601:139-43.
30. Jiang YX, Cao Q, Sawaya MR, Abskharon R, Ge P, DeTure M, *et al*. Amyloid fibrils in FTLD-TDP are composed of TMEM106B and not TDP-43. Nature 2022;605:304-9.