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Biomarkers in the Early Detection and Diagnosis of Alzheimer's Disease

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ABSTRACT

Background. Alzheimer's disease (AD) accounts for 60–70% of the over 57 million dementia cases worldwide and is projected to nearly triple by 2050. Neuropathology precedes symptoms by roughly two decades, and the approval of anti-amyloid therapies has made biomarker-confirmed early diagnosis a clinical priority.

Aim. This narrative review synthesizes evidence on cerebrospinal fluid (CSF), blood, neuroimaging, genetic, retinal, and emerging molecular biomarkers for early detection of AD, framed within the 2024 revised NIA-AA biological criteria.

Material and methods. PubMed, MEDLINE, Google Scholar, the Journal of Education, Health and Sport, and Quality in Sport were searched for studies and consensus documents published between 2014 and 2026. Six mandatory references were integrated with seventeen additional peer-reviewed sources.

Results. CSF Aβ42/40, total tau, and p-tau181 remain reference-standard markers. Plasma p-tau217 has emerged as the leading minimally invasive biomarker, with areas under the curve of 0.92–0.96 against amyloid PET. Serum neurofilament light and glial fibrillary acidic

protein support staging and differential diagnosis. Amyloid and tau PET enable in vivo Braak staging; structural MRI tracks hippocampal atrophy. APOE ε4 genotyping has regained clinical relevance in the anti-amyloid era. Optical coherence tomography, metabolomics, microRNAs, and AI-driven multimodal models expand the diagnostic frontier.

Conclusions. AD can now be detected biologically before symptoms become disabling. Translating plasma assays and AI-supported imaging into routine practice is the central challenge of the coming decade.

Key words. Alzheimer's disease, biomarkers, early diagnosis, p-tau217, amyloid PET, optical coherence tomography, neurodegeneration.

1. Introduction

Alzheimer's disease (AD) has emerged as the defining neurological challenge of the demographic transition. Globally, more than 57 million people lived with dementia in 2021, and AD is estimated to account for 60–70% of these cases1. The Global Burden of Disease Study projects that the number of people with dementia will rise to 153 million by 2050, with nearly 10 million new cases each year 1, 2. In the United States alone, approximately 7.2 million adults aged 65 years or older currently live with Alzheimer's dementia, and the figure is expected to reach 13.8 million by 2060 in the absence of effective preventive interventions 3. Total dementia care costs exceeded US$1.3 trillion in 2019, of which roughly half was attributable to informal caregiving provided overwhelmingly by women 1, 4.

For most of the twentieth century, AD was diagnosed clinically and confirmed only at autopsy. Histopathological examination of post-mortem tissue, supported by immunohistochemical staining, demonstrates the two pathognomonic lesions: extracellular β-amyloid plaques and intracellular neurofibrillary tangles formed by hyperphosphorylated tau5. Cichacz-Kwiatkowska et al. (2016) emphasize that immunohistochemistry, employing both polyclonal and monoclonal antibodies of high sensitivity and specificity, can detect, locate, and mark the changes related to Alzheimer's neurodegeneration with a precision that pure morphological staining cannot achieve 5. However, this gold standard is by definition retrospective; it confirms the disease only when the opportunity for therapeutic intervention has long passed.

The conceptual shift over the past decade has been profound. The 2018 NIA-AA Research Framework redefined AD as a biological process documented by biomarkers rather than a clinical syndrome, organising biomarkers into three pathologic domains: β-amyloid deposition (A), pathologic tau (T), and neurodegeneration or neuronal injury (N) — the AT(N) classification 6. The 2024 revised NIA-AA criteria extended this framework, introducing Core 1 biomarkers (amyloid and phosphorylated tau in biofluids) that are sufficient to establish a diagnosis of AD, and Core 2 biomarkers (tau neurofibrillary tangles measured by imaging) that support biological staging 7. For the first time, plasma assays have been formally incorporated into the criteria, with a recommended diagnostic-accuracy threshold of approximately 90% against reference standards 7.

Strużek et al. (2025) note that advances in the understanding of AD pathophysiology have enabled the detection of neurodegenerative changes even before clinical symptoms appear, allowing identification during compensatory neuroplastic stages and opening a long latent

window for intervention 8. This change of paradigm has acquired immediate clinical urgency. The 2023–2024 regulatory approvals of lecanemab and donanemab — anti-amyloid monoclonal antibodies that demonstrably slow cognitive decline in early AD — restrict treatment to patients with biomarker-confirmed amyloid pathology, either by amyloid positron emission tomography (PET) or by CSF or plasma assay 9, 10. Biomarkers, once a research instrument, now gate access to disease-modifying therapy.

This review synthesizes the current evidence on biomarkers used for early detection and diagnosis of AD across six broad domains: cerebrospinal fluid markers, blood-based assays, neuroimaging, genetic predisposition, retinal imaging, and emerging molecular signatures including metabolomics and microRNAs. The role of artificial intelligence in integrating these heterogeneous data streams is examined in a dedicated section. The goal is to provide a coherent map of where biomarker-based diagnosis stands in 2026 — what is clinically deployable, what remains research-only, and where the next clinical translation is most likely to occur.

2. Material and methods

The literature search supporting this narrative review was conducted between January and April 2026 across PubMed/MEDLINE, Google Scholar, the Journal of Education, Health and Sport (JEHS), and Quality in Sport (QS). The search strategy combined Medical Subject Headings (MeSH) and free-text keywords using the following Boolean string: ("Alzheimer's disease" OR "Alzheimer disease" OR "AD") AND ("biomarker" OR "biological marker" OR "diagnostic marker") AND ("early diagnosis" OR "preclinical" OR "mild cognitive impairment" OR "MCI") AND ("cerebrospinal fluid" OR "CSF" OR "plasma" OR "blood" OR "PET" OR "MRI" OR "optical coherence tomography" OR "OCT" OR "metabolomics" OR "microRNA" OR "APOE").

Inclusion criteria were defined as:

1.Peer-reviewed original research, meta-analyses, systematic reviews, or consensus documents.

2.Articles published between 2014 and 2026, supplemented by seminal earlier publications when foundational to the topic.

3.Studies reporting diagnostic performance metrics (sensitivity, specificity, area under the curve), pathophysiological mechanisms, or clinical implementation pathways for AD biomarkers.

4.Reports from international agencies including the World Health Organization (WHO) and Alzheimer's Disease International (ADI).

The exclusion criteria comprised non-peer-reviewed material, conference abstracts without subsequent full publication, and studies confined to animal models without translational human data, except where mechanistic context required citation. A total of twenty-three primary sources were selected for the final synthesis: six mandatory publications specified in the commissioning brief (Strużek et al. 2025; Wajda et al. 2025; Szarpak et al. 2020; Rehan et al. 2025; Cichacz-Kwiatkowska et al. 2016; Król et al. 2026) and seventeen additional peer-reviewed sources from international literature. Data were extracted into thematic sub-chapters

covering pathophysiology, the diagnostic framework, individual biomarker classes, and integrative artificial-intelligence approaches.

3. Results / State of Knowledge

3.1. Pathophysiology of Alzheimer's disease as a substrate for biomarker discovery

The molecular biology of AD underpins every biomarker currently in use. The disease is defined by the abnormal deposition of two proteins: amyloid-β (Aβ) peptides — particularly the 42-amino-acid isoform Aβ42 — which aggregate into extracellular plaques, and microtubule-associated protein tau, which accumulates intracellularly as hyperphosphorylated paired helical filaments forming neurofibrillary tangles 5, 8. Amyloid-β is generated by sequential cleavage of the amyloid precursor protein (APP) by β-secretase (BACE1) and γ-secretase. The relative production of Aβ42 versus the more soluble Aβ40 isoform determines the propensity for aggregation; Aβ42 is more hydrophobic, nucleates more rapidly, and forms the core of senile plaques 8. According to the amyloid cascade hypothesis, Aβ deposition is the earliest detectable event, followed by tau pathology, synaptic dysfunction, neuronal loss, and finally clinical symptoms. The temporal sequence — amyloid first, tau second, neurodegeneration third — is the conceptual backbone of the AT(N) framework 6.

Tau, normally a soluble microtubule-stabilizing protein, becomes pathogenic when hyperphosphorylated at multiple residues including threonine 181, threonine 217, and threonine 231. Hyperphosphorylated tau detaches from microtubules, self-aggregates into paired helical filaments, and ultimately forms neurofibrillary tangles whose distribution follows the stereotypical Braak staging pattern: trans-entorhinal cortex → limbic structures → isocortical regions 5, 19. Different phosphorylation sites become abnormal at different times: p-tau217 and p-tau231 rise earliest, tracking amyloid-driven changes, while p-tau181 elevations are more closely linked to subsequent tangle formation. This temporal dissociation underpins much of the recent enthusiasm for plasma p-tau217 as the earliest specific marker of AD pathophysiology 16.

Recent evidence has highlighted that AD pathology is not confined to these two proteinopathies. Neuroinflammation, mediated by reactive astrocytes and microglia, has emerged as a third pathological pillar. Glial fibrillary acidic protein (GFAP), released by reactive astrocytes, is now measurable in plasma and tracks closely with amyloid status 11. Synaptic loss, long considered the strongest correlate of cognitive decline, is captured by markers such as neurogranin, a postsynaptic protein abundant in dendritic spines of the hippocampus and cortex 12. Vascular contributions, mitochondrial dysfunction, and lipid metabolism abnormalities all leave biochemical fingerprints that are increasingly being read by metabolomic platforms 13.

Wajda et al. (2025) underscore that all the major neurodegenerative diseases share common metabolic perturbations including mitochondrial dysfunction, impaired energy metabolism, and oxidative stress, while displaying disease-specific signatures: dysregulated lipid metabolism, particularly involving ceramides and sphingolipids, alongside glucose dysregulation, characterizes AD; xanthine and kynurenine pathway disruption characterizes Parkinson's disease 13. This perspective is critical because it reframes AD not as a monogenic protein deposition disease, but as a systemic metabolic disorder with brain-dominant

manifestations. Each pathological process generates candidate biomarkers, and the diagnostic task is to combine them into accurate, accessible, and clinically actionable assays.

3.2. The diagnostic framework: from clinical syndrome to biological disease

3.2.1. The 2018 AT(N) framework

The 2018 NIA-AA Research Framework, authored by Jack and colleagues, formalized a fundamental shift: AD is no longer defined by its clinical consequences but by its underlying pathology, documented in vivo by biomarkers 6. Three pathological domains were identified: A (β-amyloid pathology, indexed by amyloid PET or CSF Aβ42/40), T (pathologic tau, indexed by tau PET or CSF p-tau), and N (neurodegeneration, indexed by structural MRI atrophy, FDG-PET hypometabolism, or CSF total tau) 6. Each domain was rated as positive or negative, generating a biomarker profile such as A+T+N+ (Alzheimer's continuum, with neurodegeneration) or A+T−N− (Alzheimer's pathologic change without tau or neurodegeneration). Importantly, the framework was designed for research and explicitly cautioned against direct clinical application until biomarker performance and access had matured 6.

3.2.2. The 2024 NIA-AA revision

The 2024 revised criteria, published by Jack et al., translated the research framework into criteria intended to inform clinical practice, particularly given the arrival of disease-modifying therapy 7. Biomarkers are now grouped into Core 1 (A and T1 — amyloid PET, CSF Aβ42/40, plasma Aβ42/40, plasma p-tau, CSF p-tau) and Core 2 (T2 — tau PET, reflecting neurofibrillary pathology that becomes abnormal later in disease) 7. Notably, an abnormal Core 1 biomarker is now sufficient to establish a diagnosis of AD and to inform clinical decision-making, even in cognitively unimpaired individuals when supported by clinical context 7.

The framework also expanded into a multimodal profile (AT1T2NISV) that incorporates inflammation (I), synaptic dysfunction (S), and vascular pathology (V), reflecting the increasingly polyaetiological understanding of dementia 7. Plasma biomarkers were formally included for the first time, with a stipulated diagnostic accuracy threshold of approximately 90% against reference CSF or PET standards before clinical deployment 7. Strużek et al. (2025) emphasize that biomarker abnormalities in asymptomatic individuals suggest a long latent period during which compensatory neuroplastic mechanisms maintain cognition, providing a critical window for secondary prevention 8.

3.3. Cerebrospinal fluid biomarkers

CSF analysis remains the reference standard against which all other fluid biomarkers are calibrated. Lumbar puncture provides direct access to the central nervous system extracellular space, and the resulting concentrations reflect ongoing pathology with high fidelity. Szarpak et al. (2020) note, however, that lumbar puncture carries non-trivial risk, including bleeding into the spinal cord, infection, and nerve damage, which has motivated the search for less invasive alternatives 14.

3.3.1. Amyloid-β: Aβ42 and the Aβ42/40 ratio

Aβ42 was the first widely validated CSF biomarker. Its concentration can be reduced by as much as 50% in AD patients compared with healthy controls, a paradoxical decrease that is thought to reflect sequestration of the peptide into cerebral plaques rather than reduced production 15. The Aβ42/40 ratio, which corrects for inter-individual variability in amyloid precursor protein processing, has become the preferred metric: d'Abramo et al. (2020) report that CSF Aβ42/40 correlates almost completely with amyloid PET status and is a reliable marker at both the dementia and the mild cognitive impairment (MCI) stages 15.

3.3.2. Total tau and phospho-tau

Total tau (t-tau) reflects the intensity of neurodegeneration but is not specific to AD; it is also elevated in stroke, Creutzfeldt–Jakob disease, and traumatic brain injury 14, 15. Phosphorylated tau (p-tau), and particularly the p-tau181 isoform, is more specific to AD because hyperphosphorylation at threonine 181 is closely tied to neurofibrillary tangle pathology. CSF p-tau181 reliably distinguishes AD from other dementias and is now considered a Core 1 biomarker in the 2024 framework 7, 15. Across consolidated cohorts, the combination of low CSF Aβ42/40 with elevated p-tau181 yields diagnostic accuracy exceeding 90% versus PET-confirmed amyloid status 15.

3.3.3. Synaptic and neurodegeneration markers

CSF neurogranin has attracted particular interest as a synaptic biomarker. Tarawneh et al. (2016) demonstrated that CSF neurogranin discriminated symptomatic AD from cognitively normal controls with an area under the curve (AUC) of 0.71, comparable to tau (AUC 0.85), p-tau181 (0.81), and Aβ42 (0.77) within the same cohort, and that neurogranin levels predicted future cognitive decline independently of amyloid status 12. Neurogranin is preferentially elevated in AD relative to other neurodegenerative diseases, suggesting specificity for the synaptic dysfunction that characterizes the disease early in its course 12.

CSF neurofilament light (NfL) is a marker of axonal injury that rises across the AD continuum and in many other neurodegenerative disorders. Its lack of specificity limits its diagnostic utility but enhances its value for tracking neurodegeneration intensity, particularly in trial settings 11. Szarpak et al. (2020) specifically highlight neurofilament light, β-secretase, ubiquitin, and microRNAs as biomarkers under active investigation in their analysis 14.

3.4. Blood-based biomarkers — the new frontier

The translation of CSF assays into blood has been the single most consequential development in AD biomarker science of the last five years. Blood markers are inherently more cost-effective, less invasive, and more scalable than CSF, and they remove the principal patient barrier — fear of lumbar puncture — that limits CSF testing in primary care 11, 14.

3.4.1. Plasma p-tau217

Plasma p-tau217 has emerged as the leading minimally invasive AD biomarker. Ashton et al. (2024), in a multi-cohort study of 786 participants drawn from the WRAP, TRIAD, and SPIN cohorts, reported that a fully validated plasma p-tau217 immunoassay identified abnormal amyloid PET with an AUC of 0.92–0.96 and abnormal tau PET with an AUC of 0.93–0.97,

with performance equivalent to CSF biomarkers 16. Crucially, when applied as a three-range reference (rule-in / rule-out / intermediate), the assay reduced the need for confirmatory CSF or PET testing by approximately 80%, suggesting a tiered diagnostic pathway in which plasma triages patients to confirmatory testing only when needed 16.

Subsequent memory-clinic implementation studies have replicated these findings. Plasma p-tau217 distinguishes AD from behavioural-variant frontotemporal dementia with approximately 96% accuracy and from primary psychiatric disorders with approximately 93% accuracy, addressing one of the most difficult differential-diagnostic challenges in clinical practice 11. Critically, longitudinal studies show that plasma p-tau217 increases annually only in amyloid-positive individuals, with the steepest rises occurring in those with concurrent tau positivity, supporting its use as a disease-monitoring biomarker 16.

3.4.2. Plasma Aβ42/40

Plasma Aβ42/40 measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) detects brain amyloidosis with strong diagnostic performance and is associated with longitudinal amyloid accumulation, brain atrophy, and conversion to MCI in individuals with subjective cognitive decline 11, 16. The immunoassay-based plasma Aβ42/40 ratio has historically shown narrower fold-change between AD and controls than CSF, limiting its standalone discriminative value; mass-spectrometry-based assays largely overcome this limitation. Combined panels incorporating plasma Aβ42/40, APOE genotype, and age improve accuracy further and form the basis of several commercially available blood tests 11.

3.4.3. Serum NfL and GFAP

Fang et al. (2024) evaluated serum NfL and GFAP in a Chinese cohort of healthy controls, MCI patients, and AD patients 11. Serum levels rose progressively across the spectrum: NfL was 34.69 pg/mL in healthy controls, 44.87 pg/mL in MCI, and 47.54 pg/mL in AD; GFAP rose more steeply at 23.76, 41.31, and 63.53 pg/mL respectively 11. For diagnosing AD, GFAP alone achieved an AUC of 0.928 with 90.4% sensitivity and 82.1% specificity at a cut-off of 31.40 pg/mL, while a combined NfL + GFAP model reached an AUC of 0.931 with 78.8% sensitivity and 92.3% specificity 11. GFAP also discriminated MCI from AD at a cut-off of 46.05 pg/mL, whereas NfL did not. The authors concluded that serum GFAP has better diagnostic efficacy than NfL for AD identification, while combined testing enhances specificity 11. GFAP elevation appears more selective for AD than for other neurodegenerative diseases, suggesting it captures the astroglial response to amyloid pathology rather than generic neurodegeneration 11.

Table 1. Diagnostic performance of selected fluid biomarkers for Alzheimer's disease.

Biomarker	Matrix	Reported AUC	Sensitivity / Specificity	Reference
Aβ42/40 ratio	CSF	≈0.95 vs. amyloid PET	High concordance with PET	15
Total tau (t-tau)	CSF	≈0.85 (AD vs. controls)	~85% / ~80%	12, 15
Phospho-tau 181	CSF	≈0.81 (AD vs. controls)	~85% / ~85%	12
Neurogranin	CSF	0.71 (AD vs. controls)	Comparable to tau, p-tau, Aβ42	12

p-tau217	Plasma	0.92–0.96 vs. amyloid PET	~88% / ~84% (pooled)	16
GFAP	Serum	0.928 (AD vs. controls)	90.4% / 82.1%	11
NfL + GFAP	Serum	0.931 (AD vs. controls)	78.8% / 92.3%	11

3.5. Neuroimaging biomarkers

Imaging biomarkers translate molecular pathology into spatial maps of disease. Their unique strength is the ability to localise pathology — to particular brain regions, to particular Braak stages, and to particular times — in ways that fluid biomarkers cannot.

3.5.1. Structural MRI: hippocampal atrophy

Hippocampal atrophy on T1-weighted MRI is among the longest-established neuroimaging markers of AD. The hippocampus is one of the earliest regions to atrophy, and volume loss begins before clinically detectable symptoms 17. Schuff et al. (2009), analysing 498 participants from the Alzheimer's Disease Neuroimaging Initiative across 47 imaging centres, demonstrated measurable hippocampal shrinkage within 6 months in patients with AD and MCI, with normal elderly controls showing minimal change over the same interval 17. Increased rates of hippocampal loss were associated with the APOE ε4 allele in AD, and lower CSF Aβ42 correlated with faster hippocampal atrophy independent of genotype, integrating molecular and structural biomarkers within a single longitudinal model 17.

In current practice, hippocampal volume — quantified by automated segmentation tools — predicts conversion from MCI to AD: hippocampal volumes are largest in cognitively normal controls, intermediate in MCI non-converters, and smallest in MCI converters to AD 17. Visual rating scales such as the Scheltens medial temporal atrophy score remain widely used in clinical neuroradiology, particularly where automated tools are unavailable.

3.5.2. Amyloid PET

Amyloid PET imaging visualises brain Aβ deposition in vivo. Three 18F-labelled tracers — florbetapir (Amyvid), florbetaben (NeuraCeq), and flutemetamol (Vizamyl) — received marketing authorisation from the European Medicines Agency between 2013 and 2014 and are now in routine clinical use, particularly to confirm amyloid pathology before initiation of anti-amyloid therapy 18. Richards and Sabbagh (2014) reviewed the validation evidence for florbetaben, demonstrating that it sensitively and specifically detects β-amyloid neuritic plaques against multiple gold standards including post-mortem histopathology 18. The companion 18F-tracers florbetapir and flutemetamol have shown comparable in vivo agreement with post-mortem amyloid pathology in published validation series 18.

The original amyloid PET tracer, 11C-Pittsburgh Compound B (PIB), remains the gold-standard research tool but has limited clinical utility because of its short half-life, which restricts its use to centres with on-site cyclotrons 8. Quantification using the centiloid scale, where 0 represents young healthy controls and 100 represents typical AD dementia, has standardised amyloid burden across tracers; in the lecanemab CLARITY-AD trial, the amyloid-positivity threshold was set at 30 centiloids, and the lecanemab group achieved a 59.1-centiloid greater reduction than placebo at 18 months 9.

Clinical interpretation of amyloid PET typically follows visual reading by a trained nuclear medicine physician using tracer-specific binary positive/negative criteria, supplemented by semi-quantitative measures such as the standardised uptake value ratio (SUVR) referenced to a stable region (cerebellar grey matter or pons). The Appropriate Use Criteria, jointly developed by the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging, currently restrict amyloid PET to specific clinical scenarios: cognitive impairment of unclear aetiology, atypical clinical course, and confirmation of amyloid pathology before anti-amyloid therapy. Amyloid PET is generally not recommended in cognitively asymptomatic individuals outside research contexts because positive scans are common in advanced age (occurring in approximately 30% of cognitively normal 80-year-olds) and lack the prognostic specificity to justify the resulting psychological burden 6, 8.

3.5.3. Tau PET

Tau PET — primarily using the FDA-approved tracer 18F-flortaucipir (Tauvid) — visualises neurofibrillary tangle pathology and represents the principal Core 2 biomarker in the 2024 NIA-AA framework 7, 19. Macedo et al. (2023) reviewed how flortaucipir binding distribution can be mapped onto the original Braak histopathological staging scheme: tau pathology is restricted to the transentorhinal cortex in Braak stages I–II, spreads through medial and inferior temporal lobes in stages III–IV, and finally involves isocortical brain areas in stages V–VI 19. Flortaucipir has demonstrated sensitivities of 92.3% and specificities of 80.0% for identifying Braak stages V–VI neurofibrillary tangle pathology against post-mortem confirmation 19. Tau PET burden correlates with cognitive symptoms more closely than amyloid PET and is therefore particularly useful for staging and prognosis 19.

Table 2. Principal neuroimaging biomarkers in early AD diagnosis.

Modality	Target / signal	Clinical utility	Reference
Structural MRI	Hippocampal and medial temporal volume loss	Predicts MCI-to-AD conversion; tracks neurodegeneration (N)	17
18F-Florbetapir / florbetaben / flutemetamol PET	Cerebral β-amyloid plaques	Core 1 amyloid biomarker; required for anti-amyloid therapy eligibility	9, 18
18F-Flortaucipir PET	Neurofibrillary tangles	Core 2 biomarker; supports Braak-style biological staging	7, 19
FDG-PET	Cerebral glucose metabolism	Supports differential diagnosis (AD vs. FTD); marks neurodegeneration	6

3.6. Genetic and emerging molecular biomarkers

3.6.1. APOE ε4 genotype

The apolipoprotein E (APOE) ε4 allele is the strongest genetic risk factor for late-onset AD. Possession of one ε4 allele increases risk approximately 3-fold, and homozygosity for ε4 increases risk roughly 15-fold compared with non-carriers 20. Mechanistically, APOE ε4 impairs amyloid-β clearance, enhances tau pathology, and compromises neuronal repair 20. APOE testing was historically discouraged in clinical practice because no actionable

consequence followed identification of risk; the advent of anti-amyloid therapy has reversed this position decisively 20.

Ritchie et al. (2024) describe the new clinical role of APOE genotyping in the era of amyloid-lowering drugs 20. In the lecanemab phase 3 trial, 32.6% of ε4 homozygotes experienced amyloid-related imaging abnormalities with oedema (ARIA-E), compared with 5.4% of non-carriers; comparable enrichment was seen with donanemab 20. Consequently, the European Medicines Agency restricted lecanemab to non-homozygous patients, and most prescribing pathways now require APOE genotyping before treatment initiation. Ritchie et al. recommend a sequential workflow: clinical assessment, biomarker confirmation of amyloid pathology, genetic counselling, and APOE genotyping only in patients seeking treatment, accompanied by pretest education on risk and consent 20.

3.6.2. Metabolomics

Wajda et al. (2025) review the role of metabolomics — the systematic study of small-molecule metabolites — in identifying novel AD biomarkers 13. Using mass spectrometry and nuclear magnetic resonance spectroscopy on CSF, plasma, and brain tissue, metabolomic studies have characterised AD-specific signatures including dysregulated lipid metabolism with altered ceramide and sphingolipid profiles, glucose metabolism abnormalities consistent with brain insulin resistance, and disruption of amino-acid pathways 13. These signatures are not yet ready for clinical use but offer mechanistic insight that may identify new therapeutic targets and produce non-invasive biomarkers complementary to the amyloid-tau axis 13.

3.6.3. MicroRNAs

MicroRNAs (miRNAs) are short non-coding RNAs that regulate gene expression and circulate stably in blood, making them attractive biomarker candidates. Wei et al. (2020) reported a meta-analysis of 770 AD patients and 664 controls, finding that circulating miRNAs achieved an overall sensitivity of 0.80 (95% CI: 0.75–0.83) and specificity of 0.83, with a diagnostic odds ratio of 14 21. Specific markers include serum miR-133b (90.8% sensitivity, 74.3% specificity) and plasma miR-34a-5p and miR-545-3p, identified as candidate early biomarkers 21. miR-146a, an immune-system regulator that targets amyloid-β receptors and tau-associated proteins, has been the most consistently dysregulated miRNA across blood, CSF, and brain tissue in AD studies 21. Multi-miRNA panels combining 2–4 miRNAs achieve 75–82% accuracy for distinguishing AD from controls 21. Standardisation of pre-analytical and analytical workflows remains the principal barrier to clinical implementation.

3.7. Retinal biomarkers — the eye as a window to the brain

The retina is an embryological extension of the central nervous system, and retinal ganglion cells share metabolic, vascular, and pathological vulnerabilities with cortical neurons. Optical coherence tomography (OCT) provides micron-resolution imaging of retinal layers in seconds, and the procedure is non-invasive, inexpensive, and widely available. Król et al. (2026), in a narrative review specifically commissioned for this evidence base, outline how retinal imaging via OCT correlates meaningfully with multiple neurodegenerative conditions, including AD 22.

3.7.1. RNFL and ganglion cell layer thinning

The retinal nerve fibre layer (RNFL) — composed of the unmyelinated axons of retinal ganglion cells — is the most extensively studied OCT parameter in neurodegeneration. Król et al. (2026) report that RNFL thinning is documented in AD, Parkinson's disease, and multiple sclerosis, alongside ganglion cell complex changes that extend across multiple conditions 22. The mechanism is hypothesised to involve retrograde degeneration of retinal ganglion cell axons secondary to cortical pathology, although direct retinal Aβ deposition has also been demonstrated in post-mortem AD eyes 22.

Quantitatively, AD patients show RNFL thinning of approximately 9–12 μm relative to age-matched controls, with the superior and inferior quadrants more severely affected than the nasal and temporal sectors 22. RNFL thinning is also detectable at the MCI stage, suggesting that retinal changes track with — and may precede — cortical neurodegeneration. Macular volume and ganglion cell layer thickness correlate with hippocampal volume, providing a structural link between retinal and brain biomarkers 22.

The macular ganglion cell-inner plexiform layer (GC-IPL) is increasingly favoured over RNFL alone because it directly indexes retinal ganglion cell bodies and may be less confounded by glaucoma-related thinning patterns. Spectral-domain and swept-source OCT platforms now offer automated segmentation of individual retinal layers with reproducibility sufficient for longitudinal tracking. The accessibility of the technology — examination times of under five minutes, no contrast administration, no ionising radiation, and equipment already deployed in optometry practices worldwide — makes OCT one of the most pragmatic candidate biomarkers for population-level cognitive screening 22.

3.7.2. OCT angiography and limitations

OCT angiography (OCT-A) extends OCT to visualise retinal microvasculature without contrast, and parameters such as the foveal avascular zone area and capillary plexus density have been proposed as AD biomarkers 22. Król et al. caution that, despite encouraging signals, the principal limitation of retinal biomarkers remains non-specificity: similar findings occur across AD, Parkinson's disease, glaucoma, and multiple sclerosis, requiring careful clinical contextualisation 22. Concurrently, choroidal thickness variations have been reported in AD, and the foveal avascular zone has been investigated as a potential indicator 22. The authors conclude that OCT usage has proved to be a field that deserves more attention but that significant limitations persist before mainstream diagnostic implementation 22.

3.8. Histopathology and immunohistochemistry — the diagnostic gold standard

Despite extraordinary advances in in vivo biomarkers, the definitive diagnosis of AD remains histopathological. Cichacz-Kwiatkowska et al. (2016) review the role of immunohistochemistry in diagnosing AD, emphasising that immunohistochemical staining can detect, locate, and mark the changes related to AD neurodegeneration with both polyclonal and monoclonal antibodies of high sensitivity and specificity 5. Post-mortem tissue examination reveals the hallmark structures — amyloid plaques and intracellular fibrillar tau degeneration — in pathologically altered nervous tissue, enabling neuropathological

assessment that grades disease severity according to standardised criteria such as the Braak staging system and the CERAD plaque score 5.

The clinical role of histopathology has shifted rather than diminished. With the development of in vivo biomarkers, autopsy series now serve as the validation reference for new fluid and imaging assays — for example, the post-mortem-confirmed sensitivity of 92.3% and specificity of 80.0% reported for flortaucipir against high AD neuropathological change rests entirely on this foundation 19. Furthermore, immunohistochemistry continues to identify rare or atypical cases — including primary age-related tauopathy (PART), limbic-predominant age-related TDP-43 encephalopathy (LATE), and mixed pathologies — that fluid and imaging biomarkers cannot yet resolve.

3.9. Artificial intelligence in biomarker integration

The proliferation of biomarker classes has created a problem of integration: no single marker captures all relevant pathology, and clinical interpretation of multimodal data exceeds unaided human capacity. Rehan et al. (2025) review how artificial intelligence (AI) is reshaping AD diagnostics across three primary domains: neuroimaging analysis using deep convolutional neural networks (CNNs) for MRI segmentation and classification; genetic analysis using machine-learning methods to evaluate single-nucleotide polymorphism patterns; and behavioural biomarkers including oculo-gait measurements and retinal imaging analysis 23.

Convolutional neural networks trained on structural MRI achieve diagnostic accuracies above 90% for distinguishing AD from healthy controls in research cohorts, although performance often falls when applied to real-world clinical populations because of scanner heterogeneity and demographic shift 23. Multimodal deep-learning architectures that integrate MRI, PET, fluid biomarkers, and clinical scales perform consistently better than unimodal models, with reported AUCs of 0.95 or higher for distinguishing prodromal AD from cognitively normal controls 23. Rehan et al. specifically highlight the combination of OCT angiography with AI-based image analysis as a promising route to cost-effective, rapid, and non-invasive diagnostic pathways 23. The authors conclude that AI tools are extremely promising because they can be non-invasive and highly sensitive biomarkers, potentially enabling earlier intervention and improving patient outcomes 23.

A particularly active area of AI development is the prediction of MCI-to-AD conversion. Models trained on combined MRI, plasma p-tau217, and APOE genotype have reported conversion-prediction AUCs in the 0.85–0.92 range, providing prognostic information that no single biomarker alone delivers 16, 23. Other AI applications include automated retinal image analysis, where deep-learning models extract features from fundus photographs and OCT scans that correlate with cognitive status; speech and language analysis, where natural-language processing identifies subtle linguistic changes in spontaneous speech that precede formal cognitive impairment; and digital biomarkers from smartphones and wearable devices that track gait, sleep, and typing patterns over time 23. Rehan et al. caution that, despite the technical promise, validation studies in unselected memory-clinic populations are necessary before any AI-based diagnostic claim can be deployed clinically 23.

Important constraints remain. Most published AI models are trained on data-rich research cohorts (the Alzheimer's Disease Neuroimaging Initiative and similar), which over-represent white, highly educated, urban populations. External validation in unselected memory-clinic

populations frequently shows accuracy degradation. Regulatory pathways for AI-based diagnostics are still developing, and the 2024 NIA-AA criteria explicitly require clinician oversight of all biomarker testing, including AI-derived outputs 7.

4. Discussion

The synthesis of this evidence supports a clear conclusion: AD has become a biologically diagnosable disease decades before it becomes clinically disabling. Strużek et al. (2025) capture the central insight when they note that biomarker abnormalities precede clinical symptoms and identify a long latent window during which compensatory neuroplasticity preserves cognition8. The 2024 NIA-AA framework formalises this insight in clinical criteria: an abnormal Core 1 biomarker — most pragmatically a plasma p-tau217 result — is now sufficient to establish a biological diagnosis of AD 7.

The most consequential change of the last five years is the shift from CSF to plasma. Plasma p-tau217 achieves AUCs of 0.92–0.96 against amyloid PET reference standards — performance equivalent to CSF — at a fraction of the cost and without the procedural risks of lumbar puncture that Szarpak et al. (2020) catalogue 14, 16. The implications are structural rather than incremental: a plasma assay can be deployed in primary care, performed at first presentation of cognitive concern, and used to triage patients to confirmatory PET or CSF testing only when results are equivocal 16. Memory-clinic implementation studies report that incorporating plasma p-tau217 into routine workup leads to diagnostic revisions in approximately 30% of cases and increases overall diagnostic confidence from 65% to 79% 16.

A complex clinical paradox arises when biomarker capability outpaces therapeutic capability. Strużek et al. (2025) acknowledge that despite diagnostic advances, effective treatments to halt or reverse disease progression remain elusive 8. The 2023–2024 approvals of lecanemab and donanemab partially close this gap: in the CLARITY-AD trial, lecanemab slowed decline on the Clinical Dementia Rating-Sum of Boxes by 0.45 points over 18 months, with a 59-centiloid greater reduction in amyloid burden than placebo 9; in TRAILBLAZER-ALZ 2, donanemab significantly slowed clinical progression on the integrated AD Rating Scale over 76 weeks 10. However, both therapies carry meaningful risks of ARIA-E, especially in APOE ε4 homozygotes, and the absolute clinical benefit is modest. Biomarker-confirmed early diagnosis is now the entry criterion for these therapies 9, 10, 20.

Concurrently, the diagnostic ecosystem is becoming polyaetiological. Wajda et al. (2025) emphasise that AD shares mitochondrial dysfunction, impaired energy metabolism, and oxidative stress with other neurodegenerative diseases, and that disease-specific metabolomic signatures, particularly in lipid and sphingolipid pathways, may identify subgroups missed by amyloid-tau-centric approaches 13. Cichacz-Kwiatkowska et al. (2016) remind that immunohistochemistry remains the histopathological reference and continues to identify atypical pathologies, including LATE and PART, that fluid biomarkers cannot yet resolve 5. Król et al. (2026) caution that retinal biomarkers, while structurally elegant, suffer from non-specificity across neurodegenerative diseases 22, and Rehan et al. (2025) note that AI models, although powerful, often degrade in performance when moved from research cohorts to real-world clinical populations 23. The mature view is therefore not that any single biomarker will solve the diagnostic problem, but that multimodal integration — fluid, imaging, retinal, genetic, and metabolomic — will become the diagnostic norm.

Furthermore, equity considerations cannot be deferred. Over 60% of people with dementia live in low- and middle-income countries, where MRI, PET, and even reliable laboratory infrastructure are scarce 1. Plasma p-tau217 offers a path to equitable diagnosis precisely because it requires only venepuncture, refrigerated transport, and a centralised immunoassay laboratory 16. The Alzheimer's Disease International World Alzheimer Report 2025 highlights that 75% of WHO Member States lack a national dementia plan and that rehabilitation and structured care pathways remain underdeveloped even where diagnosis is available 2. The integration of pharmacological interventions with structured diagnostic pathways and equitable access policies, rather than the discovery of yet another marker, is the binding constraint of the next decade.

Pre-analytical variability is an underappreciated barrier to clinical translation. CSF biomarkers are sensitive to tube material (low-binding polypropylene is required), centrifugation conditions, freezing time, and immunoassay platform; even small differences in these variables can shift Aβ42/40 ratios across the diagnostic threshold 15. Plasma assays face additional challenges including haemolysis, fasting status, and time from venepuncture to processing. Standardisation initiatives — including the Global Biomarker Standardization Consortium and the International Federation of Clinical Chemistry working groups on AD biomarkers — are essential prerequisites for any large-scale deployment of plasma-based diagnostics 7, 16. Regulatory clearance of in vitro diagnostic assays for plasma p-tau217 by the United States Food and Drug Administration and European Medicines Agency is now under active consideration, and the criterion of ≥90% diagnostic accuracy specified in the 2024 NIA-AA framework is intended to guide that clearance process 7.

Cost-effectiveness modelling has begun to map the economic case for biomarker-led diagnostic pathways. A tiered approach — primary-care plasma p-tau217 screening, followed by confirmatory CSF or PET only in equivocal cases — could reduce the per-patient cost of biomarker-confirmed diagnosis by an order of magnitude relative to PET-first pathways, while expanding eligibility for early treatment. The economic argument is strongest where anti-amyloid therapy is reimbursed: every avoided false-positive treatment course represents a saving on the order of US$26,000 per patient per year, plus the avoided risk of ARIA-related morbidity. These analyses, while preliminary, support the central proposition that the bottleneck in early AD diagnosis is now operational and economic rather than scientific 3, 16.

Finally, a note on staging. The 2024 NIA-AA criteria pair biological staging (A–D) with clinical staging (asymptomatic to severe dementia), explicitly acknowledging that the two scales can be discordant due to comorbid pathology, cognitive reserve, and individual variability 7. This dual-staging approach captures the heterogeneity of AD better than either dimension alone and provides the conceptual scaffold on which precision medicine for AD can be built. Genetic markers like APOE ε4 modulate both biological progression and treatment risk, and their integration into routine workflow is a defining feature of the new era 20.

5. Conclusions

1.Alzheimer's disease is now diagnosable as a biological process decades before it becomes clinically disabling, anchored by the 2024 NIA-AA criteria that recognise an abnormal Core 1 biomarker as sufficient for diagnosis.

2.Cerebrospinal fluid Aβ42/40, total tau, and phospho-tau181 retain reference-standard accuracy, but plasma p-tau217 has emerged as the leading minimally invasive biomarker, with AUCs of 0.92–0.96 against amyloid PET and the potential to reduce confirmatory testing by approximately 80%.

3.Neuroimaging biomarkers — structural MRI for hippocampal atrophy, amyloid PET for plaque burden, and tau PET for in vivo Braak staging — provide spatial resolution of pathology that fluid biomarkers cannot match and remain essential for treatment-eligibility decisions.

4.Genetic biomarkers, particularly APOE ε4 genotype, have regained clinical relevance because they predict the safety and efficacy of anti-amyloid therapy; routine APOE testing is now recommended before treatment initiation.

5.Retinal biomarkers measured by OCT, plasma metabolomics, circulating microRNAs, and synaptic markers such as neurogranin represent the next biomarker frontier, with non-specificity across neurodegenerative diseases as the principal current limitation.

6.The translation of plasma biomarker assays into primary care, the equitable extension of biomarker-based diagnosis to low- and middle-income settings, and the multimodal integration of heterogeneous data through validated artificial-intelligence models constitute the central translational priorities of the coming decade.

Disclosure

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