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SYSTEMATIC REVIEW

DIAGNOSTIC ACCURACY OF BLOOD-BASED BIOMARKERS FOR EARLY DETECTION OF ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW

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Abstract

Introduction: Alzheimer's disease (AD) continues to impose a significant global health burden, while early detection remains limited by the reliance on invasive and costly diagnostic methods such as PET imaging and cerebrospinal fluid (CSF) analysis. Blood-based biomarkers have gained attention as a more accessible alternative. This study aims to assess the diagnostic performance of plasma p-tau217, p-tau181, and Aβ42/40 in detecting early-stage AD.

Methods: A systematic review was conducted using predefined inclusion criteria. Studies were selected if they evaluated plasma biomarkers against established reference standards (CSF biomarkers, PET imaging, or neuropathology), reported diagnostic accuracy measures, and included individuals with early cognitive impairment. Extracted data covered study characteristics, assay methods, population profiles, cutoff approaches, and longitudinal outcomes.

Results: Seventeen studies involving more than 7,000 participants were included. Plasma p-tau217 consistently demonstrated the highest diagnostic accuracy across studies, with AUC values generally exceeding 0.90. Plasma p-tau181 also showed good diagnostic performance but with greater variability, particularly in early disease stages. In contrast, Aβ42/40 alone exhibited lower and less consistent accuracy, although its performance improved when combined with phosphorylated tau biomarkers. Variability in assay platforms, population characteristics, and cutoff values contributed to heterogeneity across studies.

Conclusions: Plasma p-tau217 shows strong and consistent diagnostic performance across different populations and settings, approaching that of CSF and PET biomarkers. It holds considerable potential as a practical and minimally invasive tool for early AD detection, although further standardization is still needed.

Keywords: Alzheimer's disease; p-tau217; blood-based biomarkers; early detection; diagnostic accuracy

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Introduction

Alzheimer's disease (AD) represents a growing global health crisis, with prevalence expected to triple by 2050 as populations age worldwide.[1] The pathological cascade of AD begins decades before clinical symptom onset, creating a critical window for early intervention.[2] However, current gold standard diagnostic methods—amyloid PET imaging and

cerebrospinal fluid (CSF) analysis—face significant limitations including high cost, limited accessibility, invasiveness, and requirement for specialized infrastructure.[3] These barriers disproportionately affect low-resource settings and primary care environments where most patients initially present with cognitive complaints.[1]

The emergence of blood-based biomarkers has generated substantial enthusiasm as a scalable, minimally invasive alternative for AD detection.[4] Among candidate biomarkers, plasma phosphorylated tau (p-tau) species—particularly p-tau217 and p-tau181—and the amyloid-beta ratio (Aβ42/40) have demonstrated particular promise.[5] P-tau217 has garnered specific attention due to its closer association with amyloid-dependent tau pathology and its dynamic changes across the AD continuum.[6]

Despite rapid advances in the field, several critical gaps remain. First, the comparative diagnostic accuracy of different plasma biomarkers across diverse populations and clinical settings requires systematic evaluation.[7] Second, the performance of various assay platforms—from mass spectrometry to automated immunoassays—has not been comprehensively synthesized.[8] Third, the generalizability of findings from predominantly European and North American cohorts to other ethnic populations remains uncertain.[9] Fourth, optimal cutoff strategies that balance sensitivity and specificity while minimizing indeterminate results need clarification.[10] Fifth, the utility of plasma biomarkers for longitudinal monitoring and prediction of disease progression warrants systematic assessment.[11]

Although blood-based biomarkers have shown promising results for early Alzheimer's disease detection, findings across studies remain heterogeneous. Reported diagnostic accuracy varies depending on assay platform, population characteristics, and reference standards used. For instance, some studies report near-equivalent performance between p-tau217 and p-tau181, while others demonstrate clear superiority of p-tau217, particularly in preclinical stages. Similarly, the diagnostic value of Aβ42/40 as a standalone biomarker remains inconsistent across cohorts. This lack of consistency limits clinical translation and underscores the need for a comprehensive synthesis of the available evidence.

The novelty of this systematic review lies in its comprehensive synthesis of the most recent evidence (2020–2025) specifically focused on early AD detection populations, head-to-head comparisons of multiple biomarkers and assay platforms, inclusion of emerging data from diverse ethnic cohorts (Japanese, Chinese, multi-ethnic US populations), evaluation of multi-threshold classification strategies for clinical implementation, and synthesis of longitudinal data on biomarker trajectories.

The primary objective of this systematic review is to evaluate the diagnostic accuracy of plasma p-tau217, p-tau181, and Aβ42/40 for early detection of Alzheimer's disease pathology. Secondary objectives include: (1) comparing the performance of different biomarkers and assay platforms; (2) assessing the impact of

population characteristics and clinical settings on diagnostic accuracy; (3) evaluating multi-threshold strategies for reducing confirmatory testing; and (4) synthesizing longitudinal data on biomarker changes during disease progression.

We hypothesized that plasma p-tau217 would demonstrate superior diagnostic accuracy compared to p-tau181 and Aβ42/40 for early AD detection, with performance approaching that of established CSF and PET biomarkers. We further hypothesized that diagnostic accuracy would vary by assay platform, with mass spectrometry-based methods outperforming immunoassays, and that multi-threshold strategies would effectively minimize indeterminate results.

The findings of this review have significant implications for clinical practice, research, and healthcare policy. For clinical practice, establishing the diagnostic accuracy of blood-based biomarkers could enable widespread screening in primary care settings, earlier referral to specialty care, and more efficient allocation of expensive confirmatory testing.[1] For research, validated plasma biomarkers could serve as screening tools for clinical trial enrollment and as outcome measures for disease-modifying therapies.[12] For healthcare policy, accessible blood-based testing could reduce diagnostic disparities across geographic and socioeconomic boundaries while potentially decreasing overall healthcare costs through reduced need for PET imaging and CSF analysis (13).

Materials and Methods

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation. This systematic review was not registered in PROSPERO. However, the study followed PRISMA 2020 guidelines to ensure methodological rigor.

Criteria for Eligibility

Eligible study designs included cross-sectional, case-control, and cohort studies that reported diagnostic accuracy of plasma biomarkers. Reviews, editorials, case reports, and conference abstracts were excluded.

This systematic review aims to evaluate the Diagnostic Accuracy of Blood-Based Biomarkers for Early Detection of Alzheimer's Disease: A Systematic Review of Plasma P-Tau217, P-Tau181, and Aβ42/40.

Screening

We screened in sources based on their abstracts that met these criteria:

1. **Blood-based Biomarkers**: Does the study evaluate diagnostic accuracy of plasma p-tau217, p-tau181, or Aβ42/40 ratio for Alzheimer's disease detection?
2. **Reference Standard**: Does the study use established reference standards for Alzheimer's disease diagnosis (e.g., clinical criteria, CSF biomarkers, PET

imaging, or neuropathological confirmation)?

3. **Diagnostic Accuracy Data**: Does the study report sufficient data to calculate diagnostic accuracy measures (sensitivity, specificity, positive/negative predictive values, or area under the curve)?
4. **Target Population**: Does the study include participants with suspected cognitive impairment, mild cognitive impairment, or early-stage dementia (rather than advanced dementia or severe cognitive impairment)?
5. **Study Design**: Is the study a cross-sectional, case-control, cohort study, systematic review, or meta-analysis (rather than case reports, case series, editorials, commentaries, or conference abstracts)?
6. **Comparison Group**: Does the study include a comparison group or reference standard for assessing diagnostic accuracy?
7. **Blood-based Focus**: Does the study focus on blood-based biomarkers (rather than focusing solely on CSF or other non-blood biomarkers)?
8. **Early Detection Focus**: Does the study focus on early detection populations (rather than participants with advanced dementia or severe cognitive impairment only)?

Search Strategy

The literature search was conducted for studies published between January 2020 and March 2025.

The keywords used for this research based PICO :

Table 1. PICO

Element	P (Population)	I (Intervention)	C (Comparison)	O (Outcome)
Keyword 1	Early Alzheimer's Disease	Blood-Based Biomarkers	Reference Standard	Diagnostic Accuracy
Keyword 2	Preclinical Alzheimer's Disease	Plasma P-Tau217	Gold Standard	Sensitivity
Keyword 3	Early-Stage Dementia	Plasma P-Tau181	Amyloid PET	Specificity
Keyword 4	Mild Cognitive Impairment	Plasma Aβ42/40 Ratio	Csf Biomarkers	Area Under The Curve (AUC)

The Boolean MeSH keywords inputted on databases for this research are: *("Early Alzheimer's Disease" OR "Preclinical Alzheimer's Disease" OR "Early-Stage Dementia" OR "Mild Cognitive Impairment") AND ("Blood-Based Biomarkers" OR "Plasma P-Tau217" OR "Plasma P-Tau181" OR "Plasma Aβ42/40 Ratio") AND ("Reference Standard" OR "Gold Standard" OR "Amyloid PET" OR "Csf Biomarkers") AND ("Diagnostic Accuracy" OR "Sensitivity" OR "Specificity" OR "Area Under The Curve (AUC)")*

Data extraction

Biomarker Details:

Extract details about the plasma biomarkers tested for early Alzheimer's disease detection, including:

1. Specific biomarkers studied (p-tau217, p-tau181, Aβ42/40, or combinations)
2. Assay method/platform used (e.g., mass spectrometry, Simoa, Lumipulse, specific manufacturer)
3. Antibodies used if specified
4. Sample collection and processing protocols
5. Any assay validation data reported

Cutoff values and classification strategies (e.g., predefined thresholds, Youden index, or multi-range approaches)

were extracted and summarized in the study characteristics table where available.

Each study was mapped to the predefined primary, secondary, and tertiary objectives based on the outcomes reported.

Quality Assessment:

The methodological quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. This tool evaluates risk of bias across four domains: patient selection, index test, reference standard, and flow and timing. Each domain was rated as "low risk," "high risk," or "unclear risk" of bias. Applicability concerns were also assessed for the first three domains.

The assessment was conducted based on information reported in each study, focusing on study design, population characteristics, biomarker measurement methods, reference standards, and completeness of data reporting.

Study Population:

Extract characteristics of participants relevant to early AD detection, including:

1. Disease stages studied (cognitively normal, subjective cognitive decline, mild cognitive impairment, early dementia)
2. Sample size for each group
3. Age range and mean age
4. APOE genotype distribution if reported
5. Amyloid status (positive/negative) if known at baseline
6. Any inclusion/exclusion criteria specific to early AD populations

Reference Standard:

Extract the gold standard used to define Alzheimer's disease pathology for comparison with plasma biomarkers:

1. Primary reference method (CSF biomarkers, PET imaging, neuropathology)
2. Specific thresholds/cutoffs used for abnormal pathology
3. Secondary reference methods if multiple used
4. Time interval between plasma sampling and reference standard assessment
5. Any discordant cases between reference methods

Diagnostic Accuracy:

Extract all diagnostic performance metrics for plasma biomarkers in detecting early AD pathology:

1. Area under the curve (AUC) with 95% confidence intervals
2. Sensitivity and specificity at optimal cutoffs
3. Positive and negative predictive values
4. Overall diagnostic accuracy percentages
5. Performance for detecting different pathologies (amyloid vs tau vs both)
6. Separate metrics by disease stage if provided

Optimal Cutoffs:

Extract threshold values and cutoff strategies for plasma biomarkers in early AD detection:

1. Specific cutoff values for each biomarker (with units)
2. Method used to determine optimal cutoffs (Youden index, etc.)

3. Multi-range classification schemes if used (normal/intermediate/abnormal)
4. Percentage reduction in confirmatory testing achieved
5. Cross-cohort validation of cutoffs if reported

Comparative Performance:

Extract direct comparisons between different plasma biomarkers and assays for early AD detection:

1. Head-to-head AUC comparisons with statistical significance tests
2. Ranking of biomarker performance within the same study
3. Correlation coefficients between different assays/biomarkers
4. Performance relative to CSF biomarkers or PET imaging
5. Clinical diagnostic accuracy compared to physician assessment

Longitudinal Changes:

Extract data on how plasma biomarkers change over time in early AD:

- Annual rate of change (slope) in biomarker levels by group
- Time intervals and number of follow-up measurements
- Changes in diagnostic accuracy over time
- Progression to clinical dementia and biomarker trajectories
- Sample sizes needed to detect treatment effects based on longitudinal data

Moderating Factors:

Extract factors that influence plasma biomarker performance in early AD detection:

1. Age effects on diagnostic accuracy
2. Sex/gender differences in performance
3. APOE genotype effects
4. Clinical setting (primary care vs specialty clinics)
5. Comorbidities that affect biomarker levels
6. Technical factors affecting assay performance (batch effects, storage time)

Table 2. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Early Alzheimer's Disease" OR "Preclinical Alzheimer's Disease" OR "Early-Stage Dementia" OR "Mild Cognitive Impairment") AND ("Blood-Based Biomarkers" OR "Plasma P-Tau217" OR "Plasma P-Tau181" OR "Plasma Aβ42/40 Ratio") AND ("Reference Standard" OR "Gold Standard" OR "Amyloid PET" OR "Csf Biomarkers") AND ("Diagnostic Accuracy" OR "Sensitivity" OR "Specificity" OR "Area Under The Curve (AUC)")*	28
Semantic Scholar	*("Early Alzheimer's Disease" OR "Preclinical Alzheimer's Disease" OR "Early-Stage Dementia" OR "Mild Cognitive Impairment") AND ("Blood-Based Biomarkers" OR "Plasma P-Tau217" OR "Plasma P-Tau181" OR "Plasma Aβ42/40 Ratio") AND ("Reference Standard" OR "Gold Standard" OR "Amyloid PET" OR "Csf Biomarkers") AND ("Diagnostic Accuracy" OR "Sensitivity" OR "Specificity" OR "Area Under The Curve (AUC)")*	227
Springer	*("Early Alzheimer's Disease" OR "Preclinical Alzheimer's Disease" OR "Early-Stage Dementia" OR "Mild Cognitive Impairment") AND ("Blood-Based Biomarkers" OR "Plasma P-Tau217" OR "Plasma P-Tau181" OR "Plasma Aβ42/40 Ratio") AND ("Reference Standard" OR "Gold Standard" OR "Amyloid PET" OR "Csf Biomarkers") AND ("Diagnostic Accuracy" OR "Sensitivity" OR "Specificity" OR "Area Under The Curve (AUC)")*	563
Google Scholar	*("Early Alzheimer's Disease" OR "Preclinical Alzheimer's Disease" OR "Early-Stage Dementia" OR "Mild Cognitive Impairment") AND ("Blood-Based Biomarkers" OR "Plasma P-Tau217" OR "Plasma P-Tau181" OR "Plasma Aβ42/40 Ratio") AND ("Reference Standard" OR "Gold Standard" OR "Amyloid PET" OR "Csf Biomarkers") AND ("Diagnostic Accuracy" OR "Sensitivity" OR "Specificity" OR "Area Under The Curve (AUC)")*	7,710
Wiley Online Library	*("Early Alzheimer's Disease" OR "Preclinical Alzheimer's Disease" OR "Early-Stage Dementia" OR "Mild Cognitive Impairment") AND ("Blood-Based Biomarkers" OR "Plasma P-Tau217" OR "Plasma P-Tau181" OR "Plasma Aβ42/40 Ratio") AND ("Reference Standard" OR "Gold Standard" OR "Amyloid PET" OR "Csf Biomarkers") AND ("Diagnostic Accuracy" OR "Sensitivity" OR "Specificity" OR "Area Under The Curve (AUC)")*	553

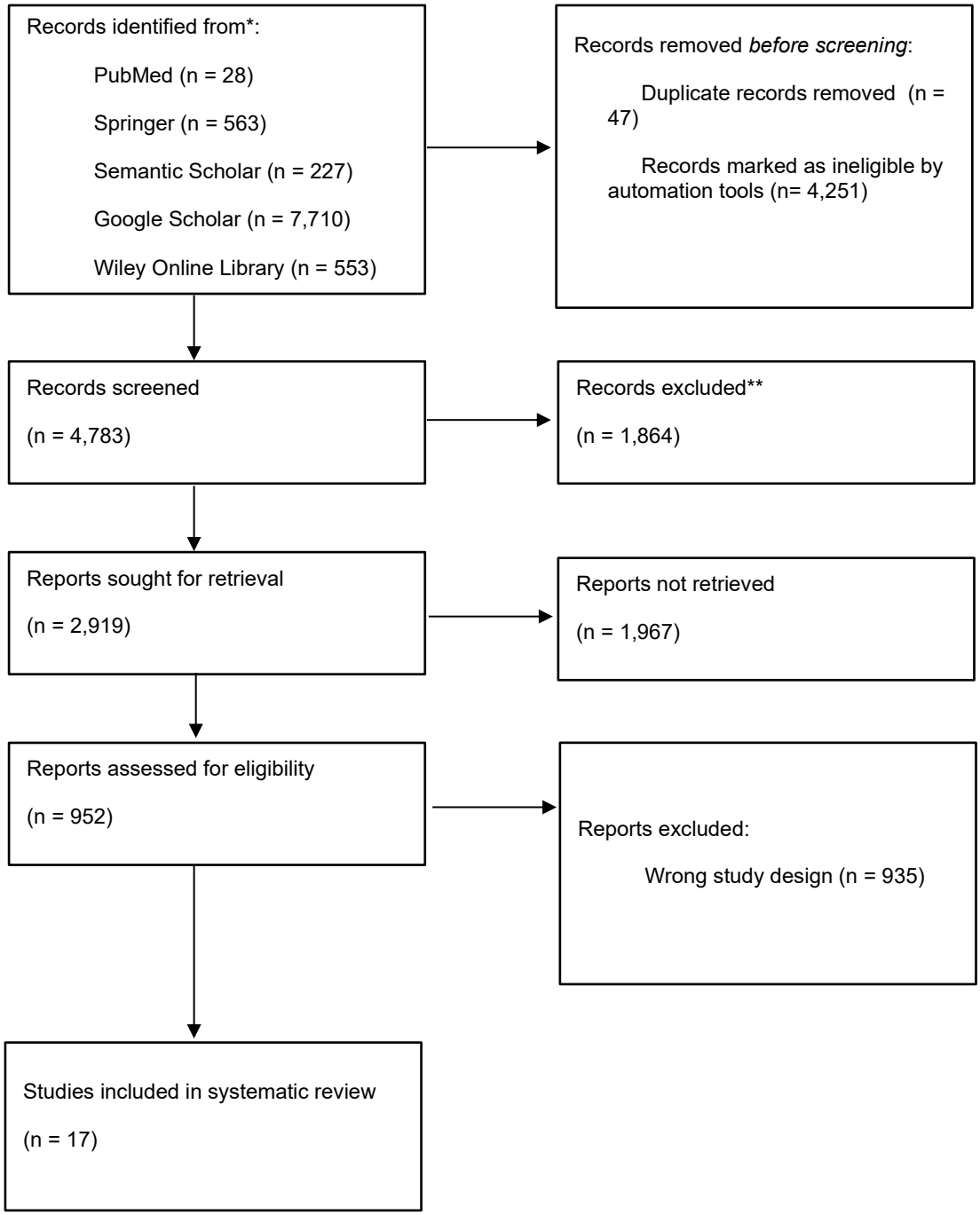

Figure 1. Article Search Flowchart

Results

Characteristics of Included Studies

This review encompasses 17 studies evaluating plasma biomarkers—primarily p-tau217, p-tau181, and Aβ42/40—for early detection of Alzheimer's disease pathology.

A total of 952 full-text articles were assessed for eligibility, of which 935 were excluded for predefined reasons. The most common reason for exclusion was inappropriate study design (e.g., reviews, editorials, case reports, or conference abstracts). Additional reasons included lack of relevant diagnostic accuracy data, absence of blood-based biomarkers, use of non-comparable reference standards, and inclusion of populations not aligned with early-stage Alzheimer's disease (e.g., advanced dementia only).

These exclusion criteria were applied to ensure that only studies directly evaluating the diagnostic performance of plasma biomarkers in early Alzheimer's disease populations were included in the final analysis.

Studies were conducted across diverse geographic settings including Sweden, the United States, Japan, China, Colombia, Canada, and multinational cohorts. The total number of unique participants across all studies exceeds 7,000, though some cohorts overlap between publications. Study designs were predominantly cross-sectional, with a subset incorporating longitudinal follow-up.

All 17 sources had full texts available for review. The studies collectively span a wide range of assay platforms, from mass spectrometry (C2N Diagnostics, Washington University nanoLC-MS/MS) to multiple immunoassay platforms (Simoa/Quanterix, Lumipulse/Fujirebio, ALZpath, Janssen, MSD, Beckman Coulter, and a novel AstraBio system). Reference standards varied across studies, including CSF biomarkers, amyloid PET, tau PET, and neuropathological confirmation, with differing thresholds for positivity (e.g., Centiloid > 20 vs. > 25 for amyloid PET).[7,12,4] Sample sizes ranged from 128 to 1,254, and populations spanned cognitively unimpaired individuals through dementia stages, with notable inclusion of non-Western cohorts from Japan, China, and a Colombian autosomal-dominant AD kindred.[6,9,8,5,10,3] A multi-ethnic community-based study in the United States (WHICAP) specifically evaluated biomarker performance across Hispanic and Black participants.[13]

Effects Diagnostic Accuracy of Plasma p-tau217

Plasma p-tau217 emerged as the most consistently high-performing individual analyte across all studies. The table below summarizes diagnostic accuracy metrics for p-tau217 (alone or as %p-tau217) across the included studies.

Table 2. Characteristics of Included Study

Study	Full Text Retrieved?	Study Type	Primary Biomarkers	Assay Platform	Sample Size	Population	Reference Standard	Cut-off Value	Cut-off Method	Outcome(s)
Sebastian Palmqvist et al., 2024	Yes	Primary study	p-tau217, Aβ42/40 (APS2)	Mass spectrometry (C2N Diagnostics)[1]	1,213[1]	SCD (23%), MCI (44%), dementia (33%); primary and secondary care [1]	CSF Aβ42:Aβ40 and p-tau217[1]	Not explicitly reported (APS2 score used)	Algorithm-based composite score	Primary objective: diagnostic accuracy Secondary objective: biomarker combination and clinical implementation
Shorena Janelidze et al., 2022	Yes	Primary study	p-tau217, p-tau181, p-tau231 (10 assays)	MS (WashU), Simoa, Lumipulse, Splex, MSD[2]	135[2]	MCI only; mean age 72.4 years[2]	CSF Aβ42/40 ratio (threshold 0.07)[2]	CSF Aβ42/40 threshold 0.07	Predefined threshold	Primary objective: diagnostic accuracy Secondary objective: head-to-head biomarker and assay comparison
Masahito Kubota et al. (n.d.)	Yes	Primary study	Aβ42/40, p-tau217, p-tau181, GFAP, NfL	HISCL (Aβ42/40), Simoa (others)[8]	243 (HC 69, preclinical AD 13, AD-MCI 38, AD-D 44, non-AD CI 79)[8]	Japanese cohort; age 40–85 years[8]	Aβ PET (CL threshold 32.90)[8]	PET CL threshold 32.90	Predefined threshold	Primary objective: diagnostic accuracy; Secondary objective: multi-biomarker evaluation
Sebastian Palmqvist et al., 2020	Yes	Primary study	P-tau217	Immunoassay (Lilly Research Laboratories)[3]	1,402 across 3 cohorts[3]	CU, MCI, AD dementia, other neurodegenerative diseases; also autosomal-dominant AD kindred.[3]	Neuropathology (cohort 1), clinical diagnosis and PET (cohort 2)[3]	Not clearly reported	Not reported	Primary objective: diagnostic accuracy; Secondary objective: disease differentiation

Study	Full Text Retrieved?	Study Type	Primary Biomarkers	Assay Platform	Sample Size	Population	Reference Standard	Cut-off Value	Cut-off Method	Outcome(s)
Matthew R Meyer et al. (n.d.)	Yes	Primary study	%p-tau217, Aβ42/40 (Precivity AD2)	LC-MS/MS[4]	583[4]	MCI (81.6%), dementia (18.4%); mean age 72.6 years[4]	Amyloid PET (CL > 25)[4]	%p-tau217 cut-off ~4.85%	Algorithm / predefined	Primary objective: diagnostic accuracy; Secondary objective: biomarker combination
Nicholas J Ashton et al., 2024	Yes	Primary study	p-tau217 (ALZpath pTau217)	ALZpath immunoassay, Simoa[11]	786[11]	CU and CI; mean age 66.3 years; 3 cohorts (TRIAD, WRAP, SPIN)[11]	Aβ PET (>24 CL), tau PET[11]	<0.4 pg/mL and >0.63 pg/mL	Three-range (dual-threshold)	Primary objective: diagnostic accuracy; Secondary objective: clinical implementation
Hyun Yoo et al. (n.d.)	Yes	Primary study	p-tau217, Aβ42, p-tau217/Aβ42 ratio	Beckman Coulter Access DxI 9000[12]	262[12]	CU, MCI, AD dementia across AD continuum[12]	Amyloid PET (CL > 20) [12]	Not explicitly stated (ratio used)	Dual-threshold approach	Primary objective: diagnostic accuracy; Secondary objective: clinical implementation
Elisabeth H Thijssen et al., 2021	Yes	Primary study	P-tau217, P-tau181	Electrochemiluminescence (MSD)[16]	566 (controls 118, MCI 99, AD 75, FTLD 274)[16]	CU, MCI, AD, FTLD[16]	Neuropathology, amyloid-PET, tau-PET[16]	Not clearly reported	Not reported	Primary objective: diagnostic accuracy; Secondary objective: disease differentiation
Adam M Brickman et al. (n.d.)	Yes	Primary study	p-tau217, p-tau181, Aβ42/40, NfL	Simoa (Quanterix), MSD[13]	413 (113 autopsied, 300 clinically evaluated)[13]	Multi-ethnic community cohort (WHICAP); mean age 81.9–85.6 years[13]	Neuropathology, amyloid PET (SUVR 1.25)[13]	Not reported	Not reported	Primary objective: diagnostic accuracy; Secondary objective: community-based evaluation

Study	Full Text Retrieved?	Study Type	Primary Biomarkers	Assay Platform	Sample Size	Population	Reference Standard	Cut-off Value	Cut-off Method	Outcome(s)
Guoping Peng et al., 2025	Yes	Primary study	p-tau217, p-tau181, Aβ42/40, GFAP, NfL	Simoa, LiCA[9]	1,254[9]	Chinese population; CU, MCI, AD dementia[9]	Aβ PET ([18F]florbetapir)[9]	≤0.37 pg/mL and >0.47 pg/mL	Dual-threshold	Primary objective: diagnostic accuracy; Secondary objective: population validation
Lu Shen et al. (n.d.)	Yes	Primary study	p-tau217, p-tau181, p-tau231, GFAP, NfL, α-synuclein	Novel single molecule array (AstraBio)[10]	668[10]	Chinese Han population; aMCI/AD (245), FTD (67), PSP (100), DLB (72), HC (184)[10]	CSF biomarkers, amyloid PET[10]	Not clearly reported	Not reported	Primary objective: diagnostic accuracy; Secondary objective: multi-biomarker comparison
Niklas Mattsson-Carlgren et al., 2020	Yes	Primary study (longitudinal)	p-tau217	Immunoassay (Lilly Research Laboratories)[15]	250 (150 CU, 100 MCI)[15]	CU (including SCD), MCI; mean age 69.5–72.7 years[15]	CSF Aβ42/40 ratio (<0.091)[15]	CSF Aβ42/40 <0.091	Predefined threshold	Primary objective: diagnostic accuracy; Tertiary objective: longitudinal analysis
Joseph Therriault et al. (n.d.)	Yes	Primary study	p-tau217 (ALZpath and Janssen)	Simoa (Janssen); ALZpath immunoassay[17]	294[17]	Young adults, CU, MCI, AD dementia, non-AD[17]	Amyloid PET (SUVR ≥1.55), tau PET (SUVR ≥1.24)[17]	Not reported	Not reported	Primary objective: diagnostic accuracy; Secondary objective: assay comparison; Tertiary objective: longitudinal analysis

Study	Full Text Retrieved?	Study Type	Primary Biomarkers	Assay Platform	Sample Size	Population	Reference Standard	Cut-off Value	Cut-off Method	Outcome(s)
Anuradha Sehrawat et al. (n.d.)	Yes	Primary study	p-tau217 (Pitt-p-tau217, ALZpath)	Simoa HD-X[14]	363[14]	CU, SCD, MCI; ADAD and sporadic AD[14]	Neuropathology (CERAD, Braak, Thal), Aβ PET, tau PET[14]	Not reported	Not reported	Primary objective: diagnostic accuracy; Secondary objective: community-based evaluation
Nicolas R Barthélemy et al. (n.d.)	Yes	Primary study	p-tau217, p-tau181	Mass spectrometry (nanoLC-MS/MS)[6]	128 (discovery 36, validation 92)[6]	Preclinical AD, MCI, controls[6]	CSF Aβ42/40 ratio (cutoff 0.139), amyloid PET[6]	CSF Aβ42/40 cutoff 0.139	Predefined	Primary objective: diagnostic accuracy; Secondary objective: biomarker validation
Suzanne E Schindler et al. (n.d.)	Yes	Primary study	p-tau217, p-tau181, Aβ42/40 (6 commercial tests)	C2N LC-MS, Fujirebio Lumipulse, ALZpath Quanterix, Janssen Quanterix, Roche NeuroToolKit[7]	392[7]	CU (200), CI (192); mean age 78.1 years; ADNI cohort[7]	Amyloid PET (CL > 20), tau PET[7]	%p-tau217 ~4.85%	Youden index	Primary objective: diagnostic accuracy; Secondary objective: assay comparison
Jun Wang et al. (n.d.)	Yes	Primary study	p-tau217, p-tau181, Aβ42/40, ratios	Lumipulse[5]	512[5]	Chinese cohorts (CADS, GHABS); preclinical, prodromal, AD dementia; mean age ~66 years[5]	Aβ PET, tau PET[5]	Not clearly reported	Not reported	Primary objective: diagnostic accuracy; Secondary objective: ratio biomarker evaluation

Note:
Cutoff values and methods were extracted where available. Several studies did not explicitly report cutoff thresholds or used algorithm-based composite scores, and are therefore indicated as "Not reported."
Primary objective: evaluation of diagnostic accuracy of plasma biomarkers. Secondary objectives: comparison between biomarkers, assay platform evaluation, and assessment across different populations. Tertiary objective: longitudinal analysis of biomarker changes.

Across all 17 studies, AUC values for plasma p-tau217 ranged from 0.84 to 0.99, with the majority of studies reporting AUCs above 0.90 for detecting amyloid pathology. The highest reported AUC was 0.99 in a small discovery cohort using mass spectrometry, while the lowest was 0.84 in a multi-ethnic community-based cohort with older participants (mean age ~85 years) and neuropathological confirmation as the reference standard.[6,13] The two largest prospective studies—Palmqvist et al., 2024 (n = 1,213) and Peng et al., 2025 (n = 1,254)—both reported AUCs of 0.92–0.97 for p-tau217-based measures, reinforcing the consistency of these findings across European and Chinese populations.[1,9]

Comparative Performance: p-tau217 vs. p-tau181 and Aβ42/40

Across studies performing direct comparisons, plasma p-tau217 consistently outperformed p-tau181 and Aβ42/40 as individual analytes. In the head-to-head comparison of 10 assays by Janelidze et al. (2022), mass spectrometry-based p-tau217 (AUC = 0.947) exhibited significantly better performance than all other plasma p-tau biomarkers for detecting abnormal Aβ status ($P < 0.015$ for all comparisons).[2] Among immunoassays in that study, p-tau217 Lilly (AUC = 0.886–0.889) outperformed several p-tau181 assays including Lumipulse (Fujirebio) and Splex (MSD), though the difference was not significant compared to p-tau181 measured by ADx or WashU MS.[2]

Schindler et al. confirmed this hierarchy in the ADNI cohort, where C2N PrecivityAD2 %p-tau217 (AUC = 0.927) outperformed Roche NeuroToolKit p-tau181 (AUC = 0.815).[7] Similarly, Wang et al. reported that plasma p-tau217 (AUC = 0.960) significantly exceeded p-tau181 (AUC = 0.942) and Aβ42/40 alone (AUC = 0.888) in a Chinese clinical cohort, Peng et al. ranked biomarker performance as p-tau217 > GFAP > p-tau181 > Aβ42/40 > NfL in the Chinese population.[5,9] In Shen et al., p-tau217 (AUC = 0.95) was the most effective biomarker for diagnosing aMCI/AD, followed by p-tau231 (AUC = 0.93) and p-tau181 (AUC = 0.83).[10] Barthélemy et al. observed a notable divergence between p-tau217 and p-tau181 in their validation cohort: while both performed equivalently in a small discovery set (AUCs of 0.99 and 0.98, respectively), p-tau217 maintained high accuracy in the larger validation cohort (AUC = 0.92) whereas p-tau181 dropped substantially (AUC = 0.75).[6] Thijssen et al. found that both P-tau217 and P-tau181 performed well when differentiating AD from controls (AUC = 0.98 vs. 0.97) and from FTLD (AUC = 0.93 vs. 0.91), with P-tau217 more strongly correlated with temporal tau-PET binding.[16]

Performance of Biomarker Combinations and Ratio Measures

Several studies evaluated composite scores and ratio measures. The APS2 score (combining %p-tau217 and Aβ42/40) demonstrated AUCs of 0.96–0.97 across primary and secondary care cohorts, with diagnostic accuracy of 88–92%.[1] However, this was not significantly different from %p-tau217 alone (diagnostic accuracy 88–91%).[1] In the ADNI cohort, models combining p-tau217 with Aβ42/40 achieved

the highest classification accuracies but were not statistically superior to p-tau217 alone.[7]

The p-tau217/Aβ42 ratio showed the highest diagnostic accuracy in the Japanese cohort (AUC = 0.946 overall, 0.979 in cognitively normal individuals), slightly exceeding both Aβ42/40 (AUC = 0.937) and p-tau217 alone (AUC = 0.926), though differences were not statistically significant.[8] Similarly, Yoo et al. found that the p-tau217/Aβ42 ratio on the Beckman Coulter platform yielded the highest AUC (0.943) and smallest indeterminate zone compared to p-tau217 alone (AUC = 0.913).[12] Wang et al. reported that plasma p-tau217/Aβ42 (AUC = 0.966) slightly outperformed p-tau217 alone (AUC = 0.960.[5] The addition of apoE proteotype to the PrecivityAD2 algorithm modestly improved performance from AUC 0.94 to 0.95 (P = 0.02).[4]

Performance Relative to CSF Biomarkers and PET Imaging

A critical finding across multiple studies is that plasma p-tau217 approaches the diagnostic accuracy of established CSF and PET-based measures. Palmqvist et al. (2020) found that plasma P-tau217 was not significantly different from CSF P-tau217, CSF P-tau181, or tau-PET in discriminating AD from other neurodegenerative diseases (AUC range 0.90–0.99 for these reference measures).[3] Ashton et al. reported comparable performance between plasma p-tau217 and CSF biomarkers in determining abnormal PET signal.[11] Wang et al. found that plasma p-tau217 and p-tau217/Aβ42 were clinically equivalent to CSF biomarkers for detecting Aβ and tau PET positivity.[5] Correlations between plasma and CSF values were strongest for mass spectrometry-based p-tau217 (R = 0.891).[2]

Notably, Palmqvist et al. (2024) demonstrated that blood tests substantially outperformed clinical assessment: primary care physicians achieved 61% diagnostic accuracy for clinical AD after standard workup (including CT scanning), compared to 91% with the APS2 blood test; dementia specialists achieved 73% versus 91%.[1]

Cutoff Strategies and Reduction in Confirmatory Testing

Multiple studies evaluated multi-threshold approaches to minimize indeterminate results and reduce the need for confirmatory invasive testing. Ashton et al. applied a three-range classification with lower and upper reference points at <0.4 pg/mL (95% sensitivity) and >0.63 pg/mL (95% specificity), which reduced confirmatory testing by approximately 80%.[11] Peng et al. used a dual-threshold approach for p-tau217 (≤0.37 pg/mL and >0.47 pg/mL), resulting in 84% of subjects having their Aβ status predicted with high accuracy, with only 16% falling in the intermediate range.[9] Yoo et al. reported intermediate zones of 13.4% for p-tau217 alone and only 8.0% for the p-tau217/Aβ42 ratio using a two-cutoff approach.[12]

Specific cutoff values varied by assay platform: Fujirebio Lumipulse p-tau217 at 0.158 pg/mL, ALZpath Quanterix at 0.462 pg/mL, C2N PrecivityAD2 %p-tau217 at 4.85%, and the Lilly immunoassay-based P-tau217 at 2.5 pg/mL.[7,3] The Youden index was the most commonly used method for determining optimal single cutoffs.[1,2,4,5,7,11]

Longitudinal Changes and Monitoring

Mattsson-Carlgren et al. (2020) provided the most detailed longitudinal data, following participants for up to 6 years with a median of three samples per person. Plasma p-tau217 showed accelerated increases in preclinical AD (β = 0.56, P < 0.001 vs. Aβ-negative controls) and prodromal AD (β = 0.67, P < 0.001), with MCI patients who later converted to AD dementia showing the highest rate of increase (β = 0.79, P < 0.001).[15] Importantly, p-tau217 did not change in Aβ-negative participants.[15] Power calculations indicated that 109 participants per arm would be required to detect a slope reduction in Aβ-positive cognitively unimpaired individuals (71 per arm for Aβ-positive MCI).[15]

Ashton et al. confirmed that plasma p-tau217 increased annually only in Aβ-positive individuals, with the highest increases in those with concurrent tau positivity (β = 0.12, P < 0.001 for A+T+ vs. β = 0.04 for A+T-).[11] In the TRIAD cohort, Therriault et al. found that annual changes in both ALZpath and Janssen p-tau217 assays correlated with annual tau PET change.[17] Sehrawat et al. reported that the AUC for discriminating tau PET-positive from tau PET-negative individuals improved from 0.52 at baseline to 0.74 at the 2-year follow-up, suggesting increasing discriminatory power over time.[14]

Cross-Platform and Cross-Assay Consistency

The head-to-head comparison by Schindler et al. across six commercial platforms demonstrated that while all p-tau217 assays outperformed p-tau181 assays, there were meaningful differences between p-tau217 platforms: C2N PrecivityAD2 %p-tau217 achieved the highest AUC (0.927), followed by Fujirebio Lumipulse (0.896), ALZpath Quanterix (0.885), and Janssen LucentAD Quanterix (0.882).[17] The mass spectrometry-based approach showed superiority, particularly in cognitively unimpaired individuals.[7] Peng et al. demonstrated cross-platform robustness in the Chinese population, with LiCA and Simoa p-tau217 assays yielding AUCs of 0.95 and 0.94, respectively.[9] The correlation between Pitt-p-tau217 and ALZpath-p-tau217 was high (ρ = 0.93), and both ALZpath and Janssen p-tau217 assays performed equivalently for identifying AD versus other neurodegenerative diseases (AUC = 0.95 and 0.96, respectively).[14,17]

Synthesis

The apparent heterogeneity in reported AUC values for plasma p-tau217 (0.84–0.99) can be substantially explained by methodological and population differences rather than representing genuine inconsistency in biomarker performance.

The highest AUC values (0.95–0.99) were observed in studies using mass spectrometry platforms or evaluating well-characterized research cohorts with clear diagnostic boundaries between groups.[2,5,6,16] The Janelidze et al. head-to-head comparison explicitly demonstrated that mass spectrometry-based p-tau217 (WashU) significantly outperformed all immunoassay-based measures, with the strongest plasma-CSF correlation (R = 0.891).[2] This suggests that a meaningful portion of inter-study variability reflects

assay methodology rather than biological variability in the biomarker itself.

The lower AUC values (0.84–0.86) were observed in specific contexts that would be expected to reduce discriminative performance. Brickman et al. reported an overall AUC of 0.84 in a community-based multi-ethnic cohort with a substantially older population (mean age 85.6 years for autopsied participants) using neuropathological confirmation as the reference standard.[13] Age-related increases in p-tau217 levels even among non-AD individuals, combined with the higher prevalence of mixed pathologies in very elderly cohorts, would reduce the separation between AD and non-AD groups.[13] Similarly, Sehrawat et al. reported AUCs of 0.82–0.84 in community-dwelling cognitively normal older adults, a population in which amyloid burden is generally lower and biomarker elevations more subtle than in clinical cohorts presenting with symptomatic impairment.[14]

The clinical setting also modulates observed performance. Palmqvist et al. (2024) found essentially equivalent diagnostic accuracy in primary care (AUC = 0.96) and secondary care (AUC = 0.97) when using standardized assay protocols, despite the higher complexity of referral populations and greater prevalence of non-AD dementias in secondary care.[1] This finding is notable because it demonstrates that plasma p-tau217 performance is robust across care settings, even though the differential diagnosis is more challenging in specialist environments.

The evidence from Chinese and Japanese cohorts provides important data on generalizability across ethnic populations. Peng et al. (n = 1,254), Shen et al. (n = 668) [10], and Wang et al. (n = 512) all reported AUCs exceeding 0.92 for p-tau217 in Chinese populations, and Kubota et al. found an AUC of 0.926 in a Japanese cohort.[9,5,8] These values are consistent with the performance ranges observed in predominantly European cohorts, though specific cutoff values differ across platforms and require local validation. In contrast, the community-based WHICAP study reported lower AUCs in its overall sample but notably high performance in Black participants (AUC = 0.96), suggesting that ethnicity per se does not attenuate biomarker performance when other factors are controlled.[13]

The distinction between p-tau217 and p-tau181 is mechanistically grounded: p-tau217 phosphorylation appears to be more closely tied to amyloid-dependent tau pathology and shows a more linear increase with disease progression, whereas p-tau181 may plateau earlier or be influenced by non-AD processes.[8] This explains the consistent finding across studies that p-tau181 performs comparably to p-tau217 in advanced disease stages (e.g., AD dementia vs. controls) but falls behind in more challenging diagnostic scenarios such as detecting preclinical amyloid positivity or distinguishing AD from other neurodegenerative diseases.[2,6,3,10]

The convergence of evidence from multiple assay platforms, geographic settings, and clinical populations indicates that plasma p-tau217—whether measured by mass spectrometry or high-performing immunoassays—achieves diagnostic accuracy in the range of 88–92% for identifying AD pathology in symptomatic populations, with performance

approaching that of CSF biomarkers and PET imaging.[1,4,5,7,3,11] In cognitively unimpaired populations, performance is more variable (AUC 0.82–0.96), reflecting the inherently greater difficulty of detecting early pathological changes in asymptomatic individuals.[8,9,14] Multi-threshold classification strategies consistently reduce the proportion of indeterminate results to 8–16% while maintaining high predictive values in definitive categories, positioning plasma p-tau217 testing as a practical triage tool that can substantially reduce the need for invasive or expensive confirmatory procedures.[9,11,12]

Discussion

This systematic review of 17 studies comprising over 7,000 participants provides a comprehensive synthesis of current evidence on blood-based biomarkers for early detection of Alzheimer's disease (AD). Overall, plasma p-tau217 demonstrated the most consistent and highest diagnostic accuracy across studies, supporting its role as a leading candidate biomarker for early AD detection. Beyond confirming its superior performance, this review also highlights important considerations related to assay variability, population characteristics, and clinical implementation.

Diagnostic Accuracy and Comparative Performance

The consistent superiority of plasma p-tau217 across diverse populations and study designs represents a robust and biologically plausible finding. This biomarker appears to more closely reflect amyloid-dependent tau pathology, which may explain its stronger association with core AD pathophysiological processes compared to p-tau181. While p-tau181 remains a useful biomarker, its diagnostic performance is more variable, particularly in preclinical stages, suggesting that it may be less sensitive for early detection.

Importantly, Aβ42/40 as a standalone biomarker demonstrated lower and less consistent diagnostic performance across studies. However, its utility improves when combined with phosphorylated tau markers, supporting the growing evidence that multi-biomarker approaches may provide superior diagnostic accuracy compared to single-marker strategies. These findings reinforce the concept that p-tau217 is currently the most reliable blood-based biomarker for early AD detection, particularly in preclinical and prodromal stages.

Our findings are consistent with previous systematic reviews that have reported the superior diagnostic performance of plasma p-tau217 compared to other blood-based biomarkers. However, compared to earlier reviews, the present study incorporates more recent evidence and includes a broader range of assay platforms and populations. In addition, this review highlights emerging classification strategies, such as dual-threshold and three-range approaches, which have been less extensively discussed in prior reviews but are highly relevant for clinical implementation.

Assay Platform Considerations

This review demonstrates that assay methodology plays a critical role in determining diagnostic performance. Mass spectrometry-based platforms generally

achieved the highest accuracy, likely due to their higher analytical specificity and reduced interference. However, several automated immunoassay platforms also demonstrated excellent diagnostic performance, indicating that clinically useful accuracy can be achieved with more scalable and accessible technologies.

The strong correlation between different assay platforms suggests that, despite methodological differences, the measurement of p-tau217 remains robust across technologies. Nevertheless, variability in assay calibration and measurement techniques underscores the need for standardization before widespread clinical adoption.

Population Characteristics and Generalizability

The variability in diagnostic performance observed across studies is largely attributable to differences in population characteristics rather than intrinsic inconsistency of the biomarker. Factors such as age, disease stage, and comorbidities influence biomarker levels and may affect diagnostic accuracy.

Importantly, the evidence supports good generalizability across different populations, including studies conducted in Asian and multi-ethnic cohorts, which demonstrated comparable diagnostic performance to predominantly European populations. However, performance tends to be lower in community-based and cognitively unimpaired populations, reflecting the greater challenge of detecting early pathological changes in asymptomatic individuals.

Sources of Heterogeneity and Study Quality

Several factors contribute to inter-study heterogeneity, including differences in assay platforms, population characteristics, reference standards, and cutoff determination methods. Variability in the use of amyloid PET versus cerebrospinal fluid biomarkers as reference standards further complicates direct comparison across studies.

Based on the QUADAS-2 assessment, the overall methodological quality of the included studies was considered to be moderate to high. Most studies demonstrated low risk of bias in the index test and reference standard domains, supporting the reliability of the reported diagnostic accuracy. However, some concerns were identified in patient selection, particularly in studies using case–control designs or selected populations, which may lead to overestimation of diagnostic performance.

Multi-Threshold Strategies and Clinical Implementation

An important development highlighted in this review is the use of multi-threshold classification strategies to improve clinical applicability. Dual-threshold and three-range approaches reduce the proportion of indeterminate results while maintaining high sensitivity and specificity, thereby minimizing the need for confirmatory testing.

These strategies have significant clinical implications, as they may allow a substantial proportion of individuals to be accurately classified using blood-based testing alone. This could reduce reliance on

more invasive or expensive diagnostic procedures, such as PET imaging or cerebrospinal fluid analysis, and facilitate broader implementation in routine clinical practice.

Longitudinal Changes and Disease Monitoring

Longitudinal data indicate that plasma p-tau217 is not only a diagnostic biomarker but also a dynamic marker of disease progression. Increases in p-tau217 levels over time are observed primarily in individuals with underlying amyloid pathology, supporting its specificity for AD.

These findings suggest that plasma p-tau217 may be useful for monitoring disease progression and evaluating treatment response, particularly in clinical trials. However, further longitudinal studies are needed to validate its role in routine clinical monitoring.

Comparison with Reference Standards

A key finding across multiple studies is that plasma p-tau217 approaches the diagnostic performance of established reference standards, including amyloid PET and cerebrospinal fluid biomarkers. This has important implications for clinical practice, as blood-based biomarkers offer a less invasive and more accessible alternative.

The integration of plasma biomarkers into diagnostic workflows could improve early detection and reduce diagnostic delays, particularly in settings where access to advanced imaging or lumbar puncture is limited.

Limitations

This systematic review has several limitations. First, heterogeneity in study design, population characteristics, assay platforms, and reference standards may limit comparability across studies. Second, variability in cutoff values and classification strategies complicates the interpretation and generalizability of diagnostic thresholds. Third, many included studies were conducted in research or specialized settings, which may not fully reflect real-world clinical populations. Fourth, this review was not prospectively registered in PROSPERO, which may introduce potential reporting bias. Finally, although a comprehensive search strategy was applied, the possibility of publication bias cannot be excluded.

Future Directions

Future research should focus on standardizing assay methods and establishing universally applicable cutoff values to facilitate clinical implementation. In addition, prospective validation in diverse and real-world populations is needed to confirm generalizability. Further studies should also explore the added value of multi-biomarker approaches and investigate the role of plasma biomarkers in guiding early therapeutic interventions.

Conclusion

This systematic review provides comprehensive evidence that plasma p-tau217 demonstrates high diagnostic accuracy for early detection of Alzheimer's disease pathology across diverse populations and clinical settings. The key findings can be summarized as follows:

First, plasma p-tau217 consistently outperforms other blood-based biomarkers including p-tau181 and Aβ42/40, with the majority of studies reporting AUC values above 0.90 for detecting amyloid pathology. This superiority is biologically grounded in p-tau217's closer association with amyloid-dependent tau pathology and its dynamic changes across the AD continuum.

Second, mass spectrometry-based assays achieve the highest diagnostic accuracy, but automated immunoassays demonstrate clinically useful performance with AUCs of 0.885–0.95, supporting their potential for widespread implementation. The strong correlations between different p-tau217 assays suggest that platform differences, while meaningful, do not preclude clinical utility.

Third, the evidence demonstrates excellent generalizability across European, North American, and Asian populations, with studies from China and Japan reporting performance metrics consistent with Western cohorts. The multi-ethnic WHICAP study's finding of particularly high performance in Black participants suggests that ethnicity does not attenuate biomarker accuracy when other factors are controlled.

Fourth, multi-threshold classification strategies consistently reduce indeterminate results to 8–16% while maintaining high predictive values, positioning plasma p-tau217 testing as a practical triage tool that could reduce the need for invasive confirmatory procedures by up to 80%. This has profound implications for healthcare resource utilization and access to diagnosis.

Fifth, longitudinal data demonstrate that plasma p-tau217 increases annually only in Aβ-positive individuals, with the highest increases in those progressing to dementia. These findings support the utility of plasma p-tau217 for monitoring disease progression, predicting clinical outcomes, and serving as an outcome measure in clinical trials.

Sixth, plasma p-tau217 approaches the diagnostic accuracy of established CSF biomarkers and PET imaging, suggesting that blood-based testing could serve as an accessible alternative to these expensive and invasive procedures in many clinical contexts.

Clinical Recommendations: Based on the evidence synthesized in this review, we recommend: (1) incorporation of plasma p-tau217 testing into diagnostic pathways for individuals with cognitive complaints, particularly in primary care settings where access to specialty evaluation is limited; (2) use of multi-threshold strategies with clearly defined cutoff values to minimize indeterminate results and guide referral for confirmatory testing; (3) platform-specific validation of cutoff values before clinical implementation; (4) interpretation of results in the context of age, clinical presentation, and relevant comorbidities; and (5) consideration of plasma p-tau217 for screening and monitoring in clinical trials of disease-modifying therapies. **Research Recommendations:** Priority areas for future investigation include: (1) standardization of assay protocols and cutoff values across platforms; (2) prospective validation in unselected primary care populations; (3) investigation of comorbidities affecting plasma p-tau levels; (4) head-to-head comparisons of leading commercial assays; (5)

development of multi-biomarker algorithms; (6) health economic analyses; (7) studies in under-represented global populations; and (8) integration with digital cognitive assessments.

In conclusion, plasma p-tau217 represents a transformative advancement in Alzheimer's disease diagnostics, offering the potential for accurate, accessible, and scalable early detection. Its performance approaching that of CSF and PET biomarkers, combined with the practicality of blood-based testing, positions it as a cornerstone of future AD diagnostic pathways. As disease-modifying therapies become available, the ability to identify individuals in the earliest stages of pathology will be essential for maximizing treatment benefit and ultimately reducing the global burden of Alzheimer's disease.

Conflict of Interest

The authors declare no conflict of interest.

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