Asia Pacific Science Press

Asia Pacific Journal of Clinical Medical Research
ISSN(O):3079-8345
ISSN(P):3079-8337
Vol. 1 No.3 (2025)

Clinical Translation of Molecular Biomarkers in Alzheimer's Disease: From Pathological Detection to Precision Medicine

Zhizhen Li [1]*, Zhaohai Feng [2], Song He [1]*, Huaping Tang [3], Cai Zhao [1], Jinfeng Liu [1], Yao Su [1], Jiayang Duan [1], Xue Tian [1], Yong Yan [1], Xiaojing Shi [1], Xueling Bi [1]

1.Maanshan Center for Clinical Laboratory, Maanshan People's Hospital, Maanshan, 243000, China.

2. Department of Neurology, Maanshan People's Hospital, Maanshan, 243000, China.

3. Department of Gerontology, Maanshan People's Hospital, Maanshan, 243000, China.

Corresponding author: Zhizhen Li, 1172163752@qq.com (LZ); Song He, jarm190@163.com (HS)

Abstract: Alzheimer's disease (AD), as the predominant form of neurodegenerative disorders, exerts a profound impact on the health of the global elderly population. For decades, the elucidation of AD pathogenesis and the development of diagnostic and therapeutic approaches have been the focus of extensive research. Over recent years, a fundamental shift has occurred in AD diagnostics—transitioning from reliance on clinical diagnosis alone to biomarker-supported frameworks. AD biomarker research has transitioned from postmortem histopathology to in vivo detection paradigms, enabling precision diagnosis and intervention. This review synthesizes recent advances in molecular biomarkers across three domains: Fluid biomarkers, Molecular imaging and Innovative detection platforms, and also evaluates the challenges and prospects of the clinical transformation of molecular markers for AD.

Keywords: Alzheimer's Disease; Biomarkers; Clinical Translation; Precision Medicine

Published: Jul 3, 2025

DOI:https://doi.org/10.62177/apjcmr.v1i3.455

1.Introduction

Alzheimer's Disease (AD), the predominant form of neurodegenerative disorders, constitutes 60-70% of all dementia cases. The global AD population has reached over 50 million and is projected to rise to 152 million by 2050 [1]. This disease not only causes progressive cognitive decline but also imposes substantial socioeconomic burdens on affected families and healthcare systems. Traditional AD diagnosis relies primarily on clinical symptoms and neuropsychological assessments; however, by this stage, pathological changes are often irreversible [2]. Over the past decade, the diagnostic paradigm for AD has undergone a fundamental shift from purely clinical diagnosis towards biomarker-supported approaches, a transformation fully reflected in the Chinese Guidelines for the Clinical Application of Fluid Biomarkers in Alzheimer's Disease published in 2024 [3].

The core value of molecular biomarkers lies in their ability to detect early AD pathological changes 10-20 years prior to the manifestation of clinical symptoms, thereby providing a critical window for intervention. According to the AT(N) research framework (Amyloid, Tau, Neurodegeneration), molecular biomarkers are primarily classified into three major categories: β-amyloid (Aβ) deposition-related biomarkers, tau protein pathology biomarkers, and neurodegeneration/neuronal injury biomarkers [1-3]. The detection technologies for these biomarkers encompass cerebrospinal fluid (CSF) analysis, peripheral

fluid testing, and molecular imaging, collectively forming a multi-tiered detection system.

Recent breakthroughs in global AD research in 2025 across six key areas have propelled the diagnostic and therapeutic model from a "one-size-fits-all" approach towards personalized and precision medicine ("tailored to the individual") [4]. Studies demonstrated that inhibition of the metabolic enzyme IDO1 can reverse cerebral glucose metabolic dysfunction in AD patients while concurrently restoring synaptic function; furthermore, they elucidated the molecular link between hearing loss and AD. Critically, CSF proteomic analysis has classified AD into five distinct subtypes, laying the groundwork for precision medicine [4]. These advances not only deepen our understanding of AD pathogenesis but also open new avenues for the clinical application of molecular biomarkers.

This review will systematically summarize the current clinical applications and recent advances in AD molecular biomarkers from four perspectives: CSF biomarkers, blood-based biomarkers, molecular imaging techniques, and emerging biomarkers/technologies. It will further explore the associated challenges and future research directions, aiming to provide a reference for clinicians and researchers.

2.Cerebrospinal Fluid Biomarkers

2.1 Clinical Application of Core Biomarkers

Cerebrospinal fluid (CSF), due to its direct reflection of the brain's microenvironment, has long served as the "molecular repository" for AD biomarker detection. According to the 2024 Chinese Guidelines, core CSF biomarkers include Aβ42, Aβ40, phosphorylated tau protein (p-tau), and total tau protein (t-tau) [3]. These biomarkers accurately reflect the cerebral pathological alterations in AD: decreased Aβ42 concentration or a reduced Aβ42/40 ratio indicates cerebral Aβ deposition, while elevated p-tau concentration reflects tau hyperphosphorylation and neurofibrillary tangle formation [3].

In clinical practice, the diagnostic value of a single biomarker is limited, and multiplex biomarker testing has become the consensus. The guideline recommendation explicitly states: "Multiple CSF biomarkers can be used in combination for AD diagnosis, demonstrating superior diagnostic performance compared to individual CSF biomarkers. The CSF Aβ42/40 ratio and Aβ42/p-tau181 ratio exhibit better diagnostic performance for AD than Aβ42 alone (Evidence Level 1A)" [3]. This recommendation is grounded in substantial research evidence indicating that composite indices significantly enhance diagnostic specificity and sensitivity.

It is noteworthy that different p-tau epitopes possess distinct clinical significance. Beyond the classical p-tau181, emerging biomarkers such as p-tau217, p-tau231, and p-tau205 demonstrate unique advantages [5-8]. Particularly, p-tau217 shows exceptional performance in differentiating AD from other neurodegenerative disorders [5], while p-tau231 is considered an indicator of earlier pathological changes [7]. A pivotal 2025 study by the University of Pittsburgh team revealed that p-Tau262 and p-Tau356 levels are significantly elevated during the "preclinical phase" preceding neurofibrillary tangle (NFT) formation, a discovery that may further advance the AD diagnostic window [9].

2.2 Auxiliary Value of Non-AD Specific Biomarkers

In addition to core AD biomarkers, neurofilament light chain protein (NfL) and glial fibrillary acidic protein (GFAP), serving as markers of neurodegeneration and neuroinflammation, respectively, hold significant auxiliary value in AD diagnosis and management [10-12]. The Chinese Guidelines state: "Non-AD specific CSF biomarkers such as NfL and GFAP indicate pathological changes in the brain, including neurodegeneration or inflammation, reflecting the severity of AD progression, but cannot be used alone for AD diagnosis (Evidence Level 1A)" [3].

NfL, a marker of axonal damage, increases in concentration with AD progression and correlates significantly with the rate of brain atrophy and cognitive decline [13]. GFAP, reflecting astrocytic activation, is elevated early in AD and demonstrates outstanding predictive value for the conversion from mild cognitive impairment (MCI) to AD [13]. Furthermore, studies have found GFAP is significantly elevated in individuals with Aβ positivity but normal cognition, suggesting its potential for ultra-early screening [14].

2.3 Novel Biomarkers and Disease Subtyping

A landmark study employing CSF proteomic analysis of 419 AD patients and 187 healthy controls classified AD into five distinct molecular subtypes: Hyperplasticity Subtype, Innate Immune Activation Subtype, Choroid Plexus Dysfunction

Subtype, Blood-Brain Barrier Dysfunction Subtype, and RNA Dysregulation Subtype. This subtyping holds critical implications for individualized treatment [15]. For instance, patients with the Innate Immune Activation Subtype may benefit preferentially from anti-inflammatory therapies, while those with the Blood-Brain Barrier Dysfunction Subtype might require vasoprotective strategies. The Chinese Guidelines also note: "Fluid biomarkers can be used for pre-screening of clinical trial participants to exclude individuals with a low probability of AD pathology (Evidence Level 1A)" [3].

3.Blood-Based Biomarkers: Breakthroughs in Non-Invasive Detection

3.1 Advances in Plasma Aβ and p-Tau Biomarkers

Although CSF testing is reliable, the invasiveness of lumbar puncture limits its widespread application. Blood-based biomarkers, leveraging the advantages of non-invasive collection, suitability for large-scale screening, and longitudinal monitoring, have become a major research focus in recent years. The 2024 Chinese Guidelines recommend: "Blood-based biomarkers utilizing highly sensitive detection methods may be used cautiously to support AD diagnosis; however, results should be confirmed whenever possible by CSF testing or PET imaging (Expert Consensus)" [3].

Technological breakthroughs have been pivotal in advancing blood biomarkers (Table 1). The emergence of ultra-sensitive detection technologies such as Single Molecule Array (Simoa) and Immunoprecipitation coupled with Mass Spectrometry (IP-MS) has enabled the accurate quantification of extremely low concentrations of AD-related proteins in blood [16-20]. Notably, for p-Tau proteins, a highly sensitive assay developed by the University of Pittsburgh team in 2025 successfully detected plasma p-Tau262 and p-Tau356. These biomarkers can identify Tau pathology changes years earlier than current methods [9].

Plasma p-tau217 is currently one of the most extensively studied blood biomarkers. Multiple large cohort studies demonstrate that plasma p-tau217 performs nearly as well as CSF testing in differentiating AD from other neurodegenerative disorders, achieving areas under the curve (AUC) exceeding 0.95 [21-23].

Table 1: Performance Comparison of Major AD Blood Biomarker Detection Platforms

Technology Platform	Detection Principle	Sensitivity	Multiplexing Capacity	Throughput	Application Scenario
Simoa	Single Molecule Array	fg/mL	Low (≤6-plex)	Medium	Research & small-scale clinical use
NULISA	Nucleic Acid Signal Amplification	fg/mL	High (120-plex)	High	Large-scale screening & omics studies
Lumipulse®	Chemiluminescent Immunoassay	pg/mL	Low	High	Routine clinical testing
IP-MS	Immunoprecipitation-Mass Spectrometry	pg/mL	Medium	Low	Reference method & research

3.2 Value of Peripheral Metabolic and Inflammatory Biomarkers

Beyond biomarkers directly reflecting AD core pathology, peripheral metabolites and inflammatory factors provide crucial information for early AD warning and subtyping. In April 2025, a study published in Chem by a Shanghai Jiao Tong University team pioneered the development of Molecularly Resolvable Surface-Enhanced Raman Spectroscopy Molecular Group Technology (MORE SERSome). This technology integrates laser desorption/ionization mass spectrometry with SERS, enabling molecular-level resolution of serum metabolic fingerprints [24]. Applying this method, the team identified significantly altered metabolites in AD patient serum, including ergothioneine and uric acid, and constructed a SERSome-Graph Convolutional Neural Network model achieving an impressive AD discrimination AUC of 91.5% [24]. These findings not only provide a novel technology for blood-based AD diagnosis but also reveal the role of metabolic dysregulation in AD pathogenesis.

Inflammatory biomarkers also play a significant role in AD risk assessment and subtype differentiation. A 2025 study

discovered that dark microglia are twice as abundant in the brains of AD patients compared to healthy individuals. These cells produce neurotoxic lipids that accelerate the loss of synaptic connections [25]. This neuroinflammatory change manifests as alterations in specific cytokine profiles in peripheral blood, offering clues for identifying the Innate Immune Activation AD subtype.

3.3 Application Scenarios and Optimization Directions for Blood Biomarkers

The core application scenarios for blood biomarkers include [3]: Large-scale population screening: The Chinese Guidelines state: "Plasma Aβ42/40 ratio, p-tau181, and p-tau217 can be used for screening AD patients." Disease progression prediction: Plasma p-tau181, p-tau217, and Aβ42/40 ratio can predict the risk of AD progression. Therapeutic effect monitoring: Blood biomarkers are suitable for dynamic assessment of treatment efficacy in clinical trials.

However, blood biomarker testing still faces challenges related to pre-analytical variability (sample collection, storage conditions), analytical variability (differences across detection platforms), and biological variability (circadian rhythms, dietary influences). Standardization of pre-analytical workflows and harmonization of detection platforms represent critical future development directions. The Chinese Guidelines also cautiously note: "Combining blood biomarkers with AD risk factors, age, sex, APOE genotype, and neuropsychological assessments enhances AD diagnostic performance, albeit with a marginal effect" [3].

4.Molecular Imaging: Visualizing Pathological Progression

4.1 Clinical Application of Aβ-PET Imaging

Molecular imaging technologies have revolutionized the field by enabling non-invasive visualization of AD pathology in the brain, realizing "in vivo histopathology". The formal clinical adoption of the Aβ-PET tracer Florbetaben ([^{18}F]) marks the entry of AD diagnosis and treatment into the era of visualized biomarkers. The core strength of Aβ-PET lies in its ability to detect abnormal cerebral β-amyloid deposition 15-20 years prior to symptom onset [26, 27]. The clinical utility of Aβ-PET extends beyond diagnosis to include treatment response monitoring, clinical trial participant screening, and treatment decision support. However, the current high cost of Aβ-PET scans and the requirement for specialized PET equipment and radionuclide production facilities limit its widespread accessibility and adoption.

4.2 Advances in Tau-PET Imaging

Compared to Aβ-PET, the development of Tau-PET imaging has been more challenging, primarily due to the complexity of tau isoforms and their intracellular localization. Tau-PET tracers offer a more accurate reflection of tau protein distribution and density. Research indicates that tau deposition exhibits a stronger correlation with cognitive dysfunction than Aβ deposition, thereby conferring unique value to Tau-PET in predicting disease progression and assessing therapeutic efficacy [28-30]. Recent research found that combining Tau-PET imaging with CSF p-tau262/p-tau356 detection enables comprehensive monitoring of tau pathology, spanning from the soluble tau aggregate (STA) stage to neurofibrillary tangle formation [9]. This holistic monitoring capability provides critical technical support for tau-targeting disease-modifying therapies.

4.3 Comparative Analysis and Integrated Application of Multimodal Imaging

Aβ-PET, Tau-PET, and FDG-PET (reflecting cerebral glucose metabolism) each have distinct emphases, forming a complementary approach in clinical practice:

· Aβ-PET: High negative predictive value for ruling out AD diagnosis [31].

· Tau-PET: Assesses disease stage and rate of progression [30].

· FDG-PET: Reflects synaptic dysfunction and the extent of neurodegeneration [32].

Future development focuses on integrating multiple molecular imaging techniques with fluid biomarkers, genetic testing, and digital biomarkers to construct a multimodal AD assessment system, enabling precise disease subtyping and personalized intervention.

5.Emerging Biomarkers and Technological Innovations

5.1 Exploration of Biomarkers in Alternative Biofluids

Beyond blood, research on AD biomarkers in more accessible biofluids like saliva, tears, and urine has progressed. The 2024

Chinese Guidelines state: "Potential AD biomarkers include lactoferrin and exosomal miRNA in saliva, eIF4E and miRNA in tears, and elevated formaldehyde and formic acid levels as well as AD-associated neuronal thread protein (AD7c-NTP) in urine" [3]. Notably, urinary AD7c-NTP testing has been implemented in some clinical settings in China, offering advantages of complete non-invasiveness and low cost, making it suitable for large-scale preliminary screening. Studies show significantly higher urinary AD7c-NTP levels in AD patients compared to healthy controls, correlating with CSF t-tau and Aβ42 levels. However, the Guidelines cautiously note: "The clinical value of biomarkers in saliva, tears, urine, and other biofluids for AD requires further evidence" [3]. Exosome technology holds particular promise for alternative biofluid analysis. Neuron-derived exosomes carry brain-specific proteins (e.g., Aβ, Tau) and can be isolated from peripheral blood via immunocapture techniques, providing an opportunity for "liquid biopsy" [33].

5.2 Metabolomics and Multi-omics Integration

Metabolomics, through the systematic analysis of small molecule metabolites (<1500 Da), reveals metabolic pathway dysregulation in AD pathology. The MORE SERSome technology developed by the Shanghai Jiao Tong University team overcame the technical bottleneck of conventional label-free Surface-Enhanced Raman Spectroscopy (SERS) for multi-analyte detection, achieving molecular-level resolution of serum metabolic fingerprints and demonstrating the significant potential of metabolomics for precise AD diagnosis [24]. Recent research also revealed that inhibiting the metabolic enzyme indoleamine 2,3-dioxygenase 1 (IDO1) can reverse cerebral glucose metabolic dysfunction in AD patients while simultaneously restoring synaptic function [34]. This discovery not only identifies a novel therapeutic target for AD but also underscores the central role of metabolic dysregulation in AD pathogenesis.

5.3 Digital Biomarkers and Artificial Intelligence Integration

Digital Biomarkers, an emerging field, enable continuous monitoring and early warning of AD by collecting data on movement patterns, speech characteristics, and cognitive behavior via wearable devices and smartphones. Research shows that digital biomarkers based on keystroke dynamics can predict MCI risk up to 5 years in advance [35-37].

Artificial Intelligence (AI) is being integrated into molecular biomarker research for:

· Multi-omics data integration analysis: Identifying AD subtype-specific molecular networks.

· Radiomics feature extraction: Identifying subtle patterns in PET/MRI images imperceptible to the human eye.

· Predictive model construction: Such as the SERSome-Graph Convolutional Neural Network model [4, 24].

A major recent breakthrough in AD research is the achievement of molecular mechanism-based disease subtyping. This subtyping provides a biological foundation for constructing AI models, holding promise for realizing genuinely personalized precision medicine ("tailored to the individual") [15].

6.Clinical Translation Challenges and Future Prospects

6.1 Bottlenecks in Standardizing Biomarker Clinical Application

Despite significant advances in molecular biomarker research, their clinical application faces multiple challenges. Standardization is the primary bottleneck—variations in sample collection protocols, detection platforms, and interpretation criteria across different laboratories hinder the comparability of results. For instance, the coefficient of variation for CSF Aβ42 measurements can exceed 20% between platforms, potentially leading to clinical misdiagnosis [38].

Balancing cost-effectiveness presents another challenge. The high cost of Aβ-PET scans limits its accessibility. While blood testing is less expensive, its accuracy still requires improvement. The Chinese Guidelines advise: "Results from blood-based biomarkers should be confirmed whenever possible by CSF testing or PET imaging (Expert Consensus)".

Ethical and psychosocial implications also warrant serious consideration. Early AD diagnosis may induce anxiety and stigma, particularly for disease stages lacking effective treatments. Establishing comprehensive genetic counseling and psychological support systems is a necessary prerequisite for the widespread adoption of molecular biomarkers.

6.2 AD Molecular Subtyping and Precision Intervention Strategies

The proposal of AD molecular subtyping lays the groundwork for precision interventions. Intervention strategies should be tailored to specific subtypes:

· Innate Immune Activation Subtype: Utilize anti-inflammatory therapies (e.g., anti-TREM2 antibodies).

· Blood-Brain Barrier Dysfunction Subtype: Employ vasoprotective agents and blood-brain barrier stabilizers.

· RNA Dysregulation Subtype: Apply small-molecule drugs targeting RNA splicing [15].

In drug development, monoclonal antibodies have achieved major breakthroughs. In February 2025, the Washington University School of Medicine initiated a six-year AD prevention trial using remternetug (developed by Eli Lilly) to intervene in high-risk individuals 11-25 years before symptom onset. Based on the hypothesis that "intervening when amyloid-beta plaques are at their earliest stage can prevent symptoms", this trial represents a paradigm shift from symptomatic treatment towards disease modification and ultimately disease prevention [39].

Notably, the diabetes drug semaglutide has shown unexpected potential in AD research. Analysis of health records from nearly 1.1 million US patients with type 2 diabetes revealed that those treated with semaglutide for three years had an approximately 70% lower risk of developing AD compared to insulin users and a 40% lower risk compared to users of another GLP-1 receptor agonist [40]. This protective effect was more pronounced in women, offering a new perspective for metabolic intervention in AD.

6.3 Shift Towards Preventive Medicine Models

AD management is undergoing a fundamental transformation from symptomatic treatment to disease modification and, critically, primary prevention. The Washington University prevention trial, costing over $130 million with approximately $98.3 million donated by the National Institutes of Health (NIH), underscores the high priority placed on preventive strategies [39].

Lifestyle interventions hold significant value in AD prevention. Research published in a Nature journal by the California Institute for Preventive Medicine demonstrated that patients with mild cognitive impairment showed improved cognitive function and favorable biomarker trends following a regimen of strict vegetarianism, personalized exercise, yoga-based stress management, and psychological support. This indicates that healthy lifestyles can reduce neuroinflammation and promote neuronal repair [41].

7.Conclusion

The research and application of molecular biomarkers for Alzheimer's Disease are undergoing a revolutionary transformation, driving the evolution of AD diagnosis and treatment from empirical medicine to precision medicine. While CSF biomarkers continue to be optimized as the gold standard, blood-based biomarkers are gaining prominence in screening and monitoring due to their non-invasive nature. Molecular imaging technologies enable in vivo visualization of pathological changes, and emerging fields like metabolomics, multi-omics integration, and digital biomarkers are opening novel research avenues.

Recent groundbreaking advances—ranging from IDO1-mediated metabolic regulation and AD molecular subtyping to the discovery of ultra-early biomarkers like p-Tau262/p-Tau356—have not only deepened our understanding of AD's complex pathological network but also provided a scientific foundation for individualized interventions. Research from the University of Pittsburgh suggests that targeting soluble tau aggregates (STAs) before neurofibrillary tangle formation may represent a critical therapeutic window for halting AD progression [9].

Future directions for AD molecular biomarkers include:

· Technological Innovation: Enhancing detection sensitivity, reducing costs, and developing point-of-care testing (POCT) devices.

· Multimodal Integration: Constructing a comprehensive assessment framework integrating fluid biomarkers, imaging, and digital biomarkers.

· Clinical Translation: Advancing biomarker-guided personalized treatment and prevention strategies.

· Real-World Validation: Demonstrating the practical utility of biomarkers in diverse clinical settings.

With the application of tracers like Florbetaben ([^{18}F]) and the development of original technologies like MORE SERSome, Chinese researchers are making significant contributions to the field of AD molecular biomarkers. These innovative technologies, combined with international cutting-edge discoveries, will collectively propel AD management into a new era characterized by early screening, diagnosis, and intervention, ultimately achieving the historic transition from an incurable to a preventable and treatable disease.

Funding

This research was funded by the Science and Technology Plan Project in the Medical and Health Field of Maanshan City (YL-2023-43).

Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

Reference

[1] GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Public Health. 2022 Feb;7(2):e105-e125. https://doi.org/10.1016/S2468-2667(21)00249-8.

[2] Wang H, Sun M, Li W, Liu X, Zhu M, Qin H. Biomarkers associated with the pathogenesis of Alzheimer's disease. Front Cell Neurosci. 2023 Dec 7;17:1279046. https://doi.org/10.3389/fncel.2023.1279046.

[3] National Health Commission Capacity Building and Continuing Education Center; Chinese Neuroscience Society; Aging Biomarker Consortium; Writing Group for the Chinese Guideline for Clinical Application of Fluid Biomarkers for Alzheimer's Disease. [Chinese guideline for clinical application of fluid biomarkers for Alzheimer's disease(2024 edition)]. Zhonghua Yi Xue Za Zhi. 2024 Sep 10;104(35):3292-3306. Chinese. https://doi.org/10.3760/cma.j.cn112137-20240523-01174.

[4] Drew L. Alzheimer's disease: highlights from research. Nature. 2025 Apr;640(8059):S2-S3. https://doi.org/10.1038/d41586-025-01101-3.

[5] Janelidze S, Stomrud E, Smith R, Palmqvist S, Mattsson N, Airey DC, et al. Cerebrospinal fluid p-tau217 performs better than p-tau181 as a biomarker of Alzheimer's disease. Nat Commun. 2020 Apr 3;11(1):1683. https://doi.org/10.1038/s41467-020-15436-0.

[6] Karikari TK, Emeršič A, Vrillon A, Lantero-Rodriguez J, Ashton NJ, Kramberger MG, et al. Head-to-head comparison of clinical performance of CSF phospho-tau T181 and T217 biomarkers for Alzheimer's disease diagnosis. Alzheimers Dement. 2021 May;17(5):755-767. https://doi.org/10.1002/alz.12236.

[7] Ashton NJ, Benedet AL, Pascoal TA, Karikari TK, Lantero-Rodriguez J, Brum WS, et al. Cerebrospinal fluid p-tau231 as an early indicator of emerging pathology in Alzheimer's disease. EBioMedicine. 2022 Feb;76:103836. https://doi.org/10.1016/j.ebiom.2022.103836.

[8] Lantero-Rodriguez J, Montoliu-Gaya L, Benedet AL, Vrillon A, Dumurgier J, Cognat E, et al. CSF p-tau205: a biomarker of tau pathology in Alzheimer's disease. Acta Neuropathol. 2024 Jan 6;147(1):12. https://doi.org/10.1007/s00401-023-02659-w.

[9] Islam T, Hill E, Abrahamson EE, Servaes S, Smirnov DS, Zeng X, et al. Phospho-tau serine-262 and serine-356 as biomarkers of pre-tangle soluble tau assemblies in Alzheimer's disease. Nat Med. 2025 Feb;31(2):574-588. https://doi.org/10.1038/s41591-024-03400-0.

[10] Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol. 2016 Jun;15(7):673-684. https://doi.org/10.1016/S1474-4422(16)00070-3.

[11] Parnetti L. Trajectories of CSF and plasma biomarkers across Alzheimer's disease continuum: disease staging by NF-L, p-tau181, and GFAP. Neurobiol Dis. 2023 Dec;189:106356. https://doi.org/10.1016/j.nbd.2023.106356.

[12] Pelkmans W, Shekari M, Brugulat-Serrat A, Sánchez-Benavides G, Minguillón C, Fauria K, et al. Astrocyte biomarkers GFAP and YKL-40 mediate early Alzheimer's disease progression. Alzheimers Dement. 2024 Jan;20(1):483-493. https://doi.org/10.1002/alz.13450.

[13] Dark HE, An Y, Duggan MR, Joynes C, Davatzikos C, Erus G, et al. Alzheimer's and neurodegenerative disease biomarkers in blood predict brain atrophy and cognitive decline. Alzheimers Res Ther. 2024 Apr 30;16(1):94. https://doi.org/10.1186/s13195-024-01459-y.

[14] Shen XN, Huang SY, Cui M, Zhao QH, Guo Y, Huang YY, et al. Plasma Glial Fibrillary Acidic Protein in the Alzheimer Disease Continuum: Relationship to Other Biomarkers, Differential Diagnosis, and Prediction of Clinical Progression. Clin Chem. 2023 Apr 3;69(4):411-421. https://doi.org/10.1093/clinchem/hvad018.

[15] Tijms BM, Vromen EM, Mjaavatten O, Holstege H, Reus LM, van der Lee S, et al. Cerebrospinal fluid proteomics in patients with Alzheimer's disease reveals five molecular subtypes with distinct genetic risk profiles. Nat Aging. 2024 Jan;4(1):33-47. https://doi.org/10.1038/s43587-023-00550-7.

[16] Chatterjee P, Pedrini S, Doecke JD, Thota R, Villemagne VL, Doré V, et al. Plasma Aβ42/40 ratio, p-tau181, GFAP, and NfL across the Alzheimer's disease continuum: A cross-sectional and longitudinal study in the AIBL cohort. Alzheimers Dement. 2023 Apr;19(4):1117-1134. https://doi.org/10.1002/alz.12724.

[17] Lu Y, Pike JR, Chen J, Walker KA, Sullivan KJ, Thyagarajan B, et al. Changes in Alzheimer Disease Blood Biomarkers and Associations With Incident All-Cause Dementia. JAMA. 2024 Oct 15;332(15):1258-1269. https://doi.org/10.1001/jama.2024.6619.

[18] Pilotto A, Quaresima V, Trasciatti C, Tolassi C, Bertoli D, Mordenti C, et al. Plasma p-tau217 in Alzheimer's disease: Lumipulse and ALZpath SIMOA head-to-head comparison. Brain. 2025 Feb 3;148(2):408-415. https://doi.org/10.1093/brain/awae368.

[19] Janelidze S, Teunissen CE, Zetterberg H, Allué JA, Sarasa L, Eichenlaub U, et al. Head-to-Head Comparison of 8 Plasma Amyloid-β 42/40 Assays in Alzheimer Disease. JAMA Neurol. 2021 Nov 1;78(11):1375-1382. https://doi.org/10.1001/jamaneurol.2021.3180.

[20] Benedet AL, Brum WS, Hansson O; Alzheimer's Disease Neuroimaging Initiative; Karikari TK, Zimmer ER, et al. The accuracy and robustness of plasma biomarker models for amyloid PET positivity. Alzheimers Res Ther. 2022 Feb 7;14(1):26. https://doi.org/10.1186/s13195-021-00942-0.

[21] Ashton NJ, Brum WS, Di Molfetta G, Benedet AL, Arslan B, Jonaitis E, et al. Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology. JAMA Neurol. 2024 Mar 1;81(3):255-263. https://doi.org/10.1001/jamaneurol.2023.5319.

[22] Palmqvist S, Janelidze S, Quiroz YT, Zetterberg H, Lopera F, Stomrud E, et al. Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA. 2020 Aug 25;324(8):772-781. https://doi.org/10.1001/jama.2020.12134.

[23] Mattsson-Carlgren N, Collij LE, Stomrud E, Pichet Binette A, Ossenkoppele R, Smith R, et al. Plasma Biomarker Strategy for Selecting Patients With Alzheimer Disease for Antiamyloid Immunotherapies. JAMA Neurol. 2024 Jan 1;81(1):69-78. https://doi.org/10.1001/jamaneurol.2023.4596.

[24] Bi X, Qian X, Xue B, Jin C, Tang H, Ye J, et al. Molecule-resolvable SERSome for metabolic profiling. Chem. 2025April 04; 102528. https://doi.org/10.1016/j.chempr.2025.102528

[25] Flury A, Aljayousi L, Park HJ, Khakpour M, Mechler J, Aziz S, et al. A neurodegenerative cellular stress response linked to dark microglia and toxic lipid secretion. Neuron. 2025 Feb 19;113(4):554-571.e14. https://doi.org/10.1016/j.neuron.2024.11.018.

[26] Ruan D, Sun L. Amyloid-β PET in Alzheimer's disease: A systematic review and Bayesian meta-analysis. Brain Behav. 2023 Jan;13(1):e2850. https://doi.org/10.1002/brb3.2850.

[27] Rafii MS. Tau PET Imaging for Staging of Alzheimer's Disease in Down Syndrome. Dev Neurobiol. 2019 Jul;79(7):711-715. https://doi.org/10.1002/dneu.22658.

[28] Ward J, Ly M, Raji CA. Brain PET Imaging: Frontotemporal Dementia. PET Clin. 2023 Jan;18(1):123-133. doi: 10.1016/j.cpet.2022.09.010.

[29] Leuzy A, Chiotis K, Lemoine L, Gillberg PG, Almkvist O, Rodriguez-Vieitez E, et al. Tau PET imaging in neurodegenerative tauopathies-still a challenge. Mol Psychiatry. 2019 Aug;24(8):1112-1134. https://doi.org/10.1038/s41380-018-0342-8.

[30] Ossenkoppele R, van der Kant R, Hansson O. Tau biomarkers in Alzheimer's disease: towards implementation in

clinical practice and trials. Lancet Neurol. 2022 Aug;21(8):726-734. https://doi.org/10.1016/S1474-4422(22)00168-5.

[31] Weber DM, Taylor SW, Lagier RJ, Kim JC, Goldman SM, Clarke NJ, et al. Clinical utility of plasma Aβ42/40 ratio by LC-MS/MS in Alzheimer's disease assessment. Front Neurol. 2024 Mar 25;15:1364658. https://doi.org/10.3389/fneur.2024.1364658.

[32] Sakimura K, Kawai T, Nashida R, Ishida Y, Harada K, Suzuki T, et al. A novel PDHK inhibitor restored cognitive dysfunction and limited neurodegeneration without affecting amyloid pathology in 5xFAD mouse, a model of Alzheimer's disease. Alzheimers Res Ther. 2024 Sep 5;16(1):197. https://doi.org/10.1186/s13195-024-01552-2.

[33] Guo H, Yang R, Cheng W, Li Q, Du M. An Update of Salivary Biomarkers for the Diagnosis of Alzheimer's Disease. Int J Mol Sci. 2025 Feb 26;26(5):2059. https://doi.org/10.3390/ijms26052059.

[34] Minhas PS, Jones JR, Latif-Hernandez A, Sugiura Y, Durairaj AS, Wang Q, et al. Restoring hippocampal glucose metabolism rescues cognition across Alzheimer's disease pathologies. Science. 2024 Aug 23;385(6711):eabm6131. https://doi.org/10.1126/science.abm6131.

[35] Schäfer S, Herrmann J, Tovar S, Linz N, Tröger J. Speech-Based Digital Biomarkers for Alzheimer's Research. Methods Mol Biol. 2024;2785:299-309. https://doi.org/10.1007/978-1-0716-3774-6_18.

[36] Sabbagh MN, Boada M, Borson S, Chilukuri M, Doraiswamy PM, Dubois B, et al. Rationale for Early Diagnosis of Mild Cognitive Impairment (MCI) Supported by Emerging Digital Technologies. J Prev Alzheimers Dis. 2020;7(3):158-164. https://doi.org/10.14283/jpad.2020.19.

[37] Hajjar I, Okafor M, Choi JD, Moore E 2nd, Abrol A, Calhoun VD, Goldstein FC. Development of digital voice biomarkers and associations with cognition, cerebrospinal biomarkers, and neural representation in early Alzheimer's disease. Alzheimers Dement (Amst). 2023 Feb 5;15(1):e12393. https://doi.org/10.1002/dad2.12393.

[38] Bjornstal O, Rogers K, Zhang W, Delhaye R, Malone M, Unger S, et al. The impact of decreased bead count to determine concentrations of amyloid beta1-42, total-tau, and phosphorylated-tau181 in human cerebrospinal fluid using xMAP technology. J Pharm Sci. 2011 Nov;100(11):4655-63. https://doi.org/10.1002/jps.22700.

[39] Schneider T. International Alzheimer's prevention trial in young adults begins. WashU Medicine. February 4, 2025. https://medicine.washu.edu/news/international-alzheimers-prevention-trial-in-young-adults-begins/

[40] Wang W, Wang Q, Qi X, Gurney M, Perry G, Volkow ND, et al. Associations of semaglutide with first-time diagnosis of Alzheimer's disease in patients with type 2 diabetes: Target trial emulation using nationwide real-world data in the US. Alzheimers Dement. 2024 Dec;20(12):8661-8672. https://doi.org/10.1002/alz.14313.

[41] Ornish D, Madison C, Kivipelto M, Kemp C, McCulloch CE, Galasko D, et al. Effects of intensive lifestyle changes on the progression of mild cognitive impairment or early dementia due to Alzheimer's disease: a randomized, controlled clinical trial. Alzheimers Res Ther. 2024 Jun 7;16(1):122. https://doi.org/10.1186/s13195-024-01482-z.