

Artificial Intelligence-Based Biomarkers for Alzheimer's Disease: Current Advances, Challenges, and Future Directions

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ABSTRACT

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized by amyloid- β plaques and tau neurofibrillary tangles, necessitating early and accurate diagnosis for effective intervention. Recent advances in Artificial Intelligence (AI) have significantly enhanced the discovery and interpretation of AD biomarkers by enabling the integration of complex, multimodal datasets, including neuroimaging, molecular, genetic, and digital biomarkers. AI-driven approaches, particularly machine learning and deep learning, have demonstrated high accuracy in identifying early pathological changes, predicting disease progression, and distinguishing AD from mild cognitive impairment. Emerging digital biomarkers derived from speech, motor activity, cognitive tests, and wearable sensors further expand non-invasive diagnostic capabilities. Despite promising results, challenges such as data heterogeneity, lack of external validation, limited interpretability ("black-box" models), and difficulties in clinical translation remain substantial barriers. Future research is expected to focus on multimodal data fusion, explainable AI, longitudinal modelling, and personalized prediction frameworks, along with improved standardization and regulatory validation. AI-based biomarker research holds potential to transform early diagnosis, prognosis, and precision medicine in Alzheimer's disease.

Keywords: Alzheimer's Disease, Artificial Intelligence, Biomarkers, Deep learning, Early diagnosis, Machine learning.

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INTRODUCTION

Alzheimer's Disease (AD) is the most common cause of dementia, accounting for approximately 60-70% of cases worldwide. It is a progressive neurodegenerative disorder characterized by gradual cognitive decline, memory impairment, and functional deterioration, ultimately leading to loss of independence and death (Jack *et al.*, 2023). The pathological hallmarks of AD include the accumulation of extracellular amyloid- β ($A\beta$) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, which begin to develop years-often decades-before the onset of clinical symptoms (Scheltens *et al.*, 2021). Early and accurate diagnosis of AD remains a major clinical challenge. Conventional diagnostic approaches rely on neuropsychological assessments, neuroimaging techniques such as Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET), and biochemical analysis of Cerebrospinal

Fluid (CSF) biomarkers (Hampel *et al.*, 2023). While these methods provide valuable insights, they are often expensive, invasive, or limited in sensitivity during the preclinical stage of the disease. In recent years, the concept of biomarkers has become central to AD research and clinical practice. Biomarkers enable the detection of underlying pathological processes, facilitate early diagnosis, monitor disease progression, and assess therapeutic responses. Traditional biomarkers include amyloid- β , tau proteins, and structural or functional brain changes. However, these biomarkers alone may not fully capture the complexity and heterogeneity of AD. The rapid advancement of Artificial Intelligence (AI)-particularly Machine Learning (ML) and Deep Learning (DL)-has introduced new possibilities for biomarker discovery and interpretation. AI techniques can analyse large, high-dimensional datasets and identify subtle patterns that are not detectable through conventional statistical methods (Teunissen *et al.*, 2022). This capability is especially valuable in AD, where multimodal data-including neuroimaging, genomics, proteomics, and clinical assessments-must be integrated to improve diagnostic accuracy. Despite these promising developments, several challenges remain, including data heterogeneity, lack of standardization, limited model interpretability, and barriers to clinical implementation. Addressing these issues is essential for translating AI-based biomarker research into real-world healthcare applications. This



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review aims to provide a comprehensive overview of AI-based biomarkers in Alzheimer's disease, highlighting current advances, methodological approaches, challenges, and future directions toward precision medicine (Frisoni *et al.*, 2022).

METHODOLOGY

Literature Search Strategy

A comprehensive literature search was conducted to identify relevant studies on Artificial Intelligence (AI)-based biomarkers in Alzheimer's Disease (AD). Electronic database, including PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect were searched for articles published between 2017 and 2026.

Search Terms

The search strategy employed combinations of keywords and Medical Subject Headings (MeSH) terms, including: "Alzheimer's disease", "Artificial Intelligence", "Machine Learning", "Deep Learning", "Biomarkers", "Neuroimaging", "Magnetic Resonance Imaging (MRI)", "Positron Emission Tomography (PET)", "Digital Biomarkers", "Genomics", and "Early Diagnosis".

Inclusion Criteria

Studies were included if they:

- Focused on Alzheimer's disease and related cognitive disorders.
- Investigated AI, machine learning, or deep learning applications in biomarker discovery, diagnosis, prognosis, or disease monitoring.
- Reported findings related to molecular, genetic, neuroimaging, digital, or multimodal biomarkers.
- Were published in peer-reviewed journals and written in English.

Exclusion Criteria

Studies were excluded if they:

- Were conference abstracts, editorials, letters, or duplicate publications.
- Did not involve Alzheimer's disease-specific biomarkers.
- Lacked sufficient methodological or clinical information.

Data Extraction and Analysis

Relevant information including study design, biomarker type, AI methodology, dataset characteristics, diagnostic performance, and major findings was extracted and reviewed. The collected evidence was organized into thematic categories comprising molecular biomarkers, genetic biomarkers, neuroimaging biomarkers, digital biomarkers, and multimodal approaches.

Current advances, challenges, limitations, and future research directions were critically evaluated and summarized.

Ethical Considerations

As this study is a narrative review based on previously published literature, ethical approval and informed consent were not required.

Types of Biomarkers in Alzheimer's Disease

Biomarkers in Alzheimer's Disease (AD) provide measurable indicators of underlying pathological processes and are essential for early diagnosis, disease staging, and monitoring progression. With advances in technology and Artificial Intelligence (AI), multiple categories of biomarkers have been identified, each reflecting different aspects of AD pathology (Table 1).

Molecular Biomarkers

Molecular biomarkers are among the most established indicators of AD pathology and are primarily detected in Cerebrospinal Fluid (CSF) and blood.

- Amyloid- β : Reduced levels of A β 42 in CSF and increased deposition in the brain are key early indicators of AD.
- Tau proteins: Elevated Total Tau (t-tau) and Phosphorylated Tau (p-tau) reflect neuronal damage and tau pathology.
- Emerging blood-based biomarkers: Plasma A β , p-tau isoforms, and Neurofilament light chain (NfL) are gaining attention due to their minimally invasive nature (Beheshti *et al.*, 2025).
- AI techniques are increasingly used to analyse complex molecular datasets, improving sensitivity and specificity in detecting early pathological changes (Christodoulou *et al.*, 2025).

Genetic Biomarkers

Genetic factors play a significant role in AD susceptibility and progression.

- Apolipoprotein E: The APOE ϵ 4 allele is the strongest genetic risk factor for late-onset AD.
- Familial AD genes: Mutations in APP, PSEN1, and PSEN2 are associated with early-onset AD (Jiao *et al.*, 2025).
- Polygenic risk scores: AI-driven models integrate multiple genetic variants to predict disease risk more accurately.
- AI helps in identifying novel genetic patterns and interactions that contribute to disease heterogeneity (Qi *et al.*, 2025).

Neuroimaging Biomarkers

Neuroimaging provides structural and functional insights into brain changes associated with AD.

Magnetic Resonance Imaging (MRI): Detects brain atrophy, particularly in the hippocampus and cortical regions.

Positron Emission Tomography (PET): Enables visualization of amyloid and tau deposition (Zhang *et al.*, 2024).

Functional Imaging (fMRI): Assesses changes in brain connectivity and activity.

Deep learning models have shown high accuracy in analysing imaging data, enabling early detection and differentiation between AD, Mild Cognitive Impairment (MCI), and normal aging.

Digital Biomarkers

Digital biomarkers are an emerging and rapidly growing field in AD research.

- Speech and language analysis: Changes in speech patterns and vocabulary may indicate early cognitive decline.
- Motor function and gait analysis: Subtle impairments in movement can serve as early indicators.
- Cognitive performance data: Collected through mobile apps and online tests.
- Wearable sensors: Provide continuous monitoring of sleep, activity, and physiological signals.
- AI plays a crucial role in extracting meaningful patterns from these high-frequency, real-world data streams, enabling non-invasive and cost-effective monitoring (Wang *et al.*, 2025).

Multimodal Biomarkers

Single biomarkers may not fully capture the complexity of AD; therefore, combining multiple biomarker types is increasingly important.

- Integration of molecular, genetic, imaging, and digital data.
- Improved diagnostic accuracy and prediction of disease progression.
- AI-driven data fusion techniques enable comprehensive disease modelling 12 .
- Multimodal approaches are considered the future of AD diagnostics, supporting personalized and precision medicine.

Role of Artificial Intelligence in Biomarker Discovery

Artificial Intelligence (AI) has emerged as a transformative tool in Alzheimer's Disease (AD) research, particularly in the discovery, validation, and application of biomarkers. Traditional analytical methods often struggle to handle the complexity and high dimensionality of biomedical data, whereas AI techniques-especially Machine Learning (ML) and Deep Learning (DL)-enable the extraction of meaningful patterns from large, heterogeneous datasets (Table 2) (Lundberg *et al.*, 2021).

Deep Learning Techniques

Deep learning, a subset of AI, is particularly effective for analysing complex data such as neuroimaging and speech.

Convolutional Neural Networks (CNNs): Widely used for MRI and PET image analysis to detect structural and functional brain changes (Esteva *et al.*, 2019).

Recurrent Neural Networks (RNNs) and Transformers: Useful for longitudinal data and sequential patterns, such as cognitive decline over time.

Auto encoders: Enable unsupervised feature extraction and dimensionality reduction in high-dimensional datasets (Topol *et al.*, 2019).

DL models often outperform traditional methods in accuracy, especially in imaging-based diagnosis.

Machine learning approaches

Machine learning algorithms are widely used to identify relationships between biomarkers and disease outcomes.

Supervised learning: Algorithms such as Support Vector Machines (SVM), random forests, and logistic regression are trained on labelled datasets to classify individuals into AD, Mild Cognitive Impairment (MCI), or healthy controls (Wen *et al.*, 2020).

Unsupervised learning: Clustering techniques help identify hidden subtypes of AD and novel biomarker patterns without predefined labels.

Feature selection: ML methods can determine the most informative biomarkers, reduce dimensionality and improve model performance (Vieira *et al.*, 2017).

These approaches have significantly enhanced early diagnosis and risk prediction.

Advantages of AI

- Ability to process large-scale, high-dimensional data.
- Detection of subtle and complex patterns.
- Automation and scalability.

- Enhanced diagnostic accuracy and reproducibility (Davatzikos *et al.*, 2019).

Current Advances in AI-Based Biomarkers

Recent advances in Artificial Intelligence (AI) have significantly improved the diagnostic accuracy of Alzheimer's Disease (AD) through the application of Machine Learning (ML) and Deep Learning (DL) models. These models analyse complex datasets derived from Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and clinical records to detect subtle structural and functional brain changes. AI algorithms, particularly convolutional neural networks, can identify patterns such as hippocampal atrophy and amyloid deposition with higher precision than conventional methods, thereby enhancing sensitivity and reducing diagnostic errors.

One of the most important breakthroughs is the ability of AI-based biomarkers to enable early and preclinical detection of AD. By identifying disease-specific changes years before the onset of clinical symptoms, AI facilitates timely intervention and better disease management. Predictive models trained on large datasets can classify individuals at risk of developing AD, including those with Mild Cognitive Impairment (MCI), allowing clinicians to initiate preventive or disease-modifying strategies at an earlier stage (Young *et al.*, 2020).

Multimodal data integration represents another major advancement, where AI combines imaging data with genetic, molecular, and clinical information to provide a comprehensive understanding of disease pathology. This integrative approach improves prediction accuracy and supports personalized medicine by capturing the complex interactions between different biological systems (Ding *et al.*, 2020). AI-driven frameworks can synthesize diverse datasets into unified models, enabling more robust diagnosis and prognosis.

The development of digital biomarkers has further expanded the scope of AI in AD. Data collected from wearable devices, smartphones, and cognitive assessment tools are analysed using AI techniques to monitor behavioural and functional changes. Parameters such as speech patterns, gait abnormalities, sleep disturbances, and daily activity levels can serve as early indicators of cognitive decline. These non-invasive and continuous monitoring tools offer a scalable solution for real-world screening and disease tracking (Alzheimer's Association, 2024).

Challenges and Limitations

Despite remarkable progress in Artificial Intelligence (AI)-based biomarkers for Alzheimer's Disease (AD), several important challenges and limitations continue to restrict their widespread clinical application. One of the most fundamental issues is data heterogeneity. Biomarker data in AD are collected from multiple sources such as neuroimaging, genetics, cerebrospinal fluid,

blood tests, and digital platforms, but these datasets often differ in quality, acquisition protocols, and pre-processing methods. Variations across imaging scanners, laboratory techniques, and clinical assessment tools introduce inconsistencies that reduce the reliability and reproducibility of AI models. In addition, missing data and noise in real-world clinical datasets further complicate model training and validation. Another major limitation is the relatively small and imbalanced nature of available datasets (National Institute on Aging, 2025). Many AI systems are trained on limited patient samples, which may not represent the full spectrum of disease progression. In particular, early-stage and preclinical Alzheimer's cases are underrepresented, while datasets often contain more healthy controls or advanced-stage patients. This imbalance increases the risk of overfitting, where models perform well on training data but fail to generalize effectively to new populations. As a result, external validation across independent and diverse cohorts remains limited, reducing confidence in real-world performance (Ottoy *et al.*, 2025).

The lack of standardization is another significant barrier. There are currently no universally accepted guidelines for biomarker definition, data pre-processing, feature selection, or model evaluation in Alzheimer's research. Different studies often use different performance metrics and validation strategies, making it difficult to compare results across studies or replicate findings. This inconsistency slows down progress toward clinically reliable AI systems.

Table 1: Types of Biomarkers in Alzheimer's Disease and their Clinical Significance.

Biomarkers Type	Examples	Clinical Significance
Molecular Biomarkers	A β 42, t-tau, p-tau, NfL	Early diagnosis and disease monitoring
Genetic Biomarkers	APOE ϵ 4, APP, PSEN1, PSEN2	Risk prediction and genetic susceptibility
Neuroimaging Biomarkers	MRI, PET, fMRI	Detection of structural and functional brain changes
Digital Biomarkers	Speech analysis, gait assessment, wearable sensor data	Non-invasive monitoring of cognitive decline
Multimodal Biomarkers	Integration of molecular genetics, imaging, and digital Biomarkers	Improved diagnostic accuracy and personalized medicine

Abbreviations: A β 42, Amyloid-beta 42; t-tau, total tau; p-tau, phosphorylated tau; NfL, neurofilament light chain; MRI, Magnetic resonance imaging; PET, Positron Emission Tomography; fMRI, Functional Magnetic Resonance S Imaging.

Table 2: Artificial Intelligence Techniques used in Alzheimer's Disease Biomarkers Research.

AI Technique	Application	Advantages
Support Vector Machine (SVM)	Disease classification	High predictive accuracy
Random Forest	Biomarkers selection and prediction	Handles complex datasets
Logistic Regression	Risk Management	Easy interpretation
Convolutional Neural Network (CNNs)	MRI and PET image analysis	Automated features extraction
Recurrent Neural Network (RNNs)	Longitudinal disease progression analysis	Suitable for sequential data
Autoencoders	Feature extraction and dimensionality reduction	Efficient handling of high-dimensional data
Multimodal Data Fusion Models	Integration of multiple Biomarkers sources	Enhanced diagnostic performance

Abbreviations: SVM, support vector machine; CNN, convolutional neural network; RNN, recurrent neural network; XAI, Explainable Artificial Intelligence.

Overall, while AI-based biomarker research in Alzheimer's disease holds strong promise for improving early diagnosis, prediction, and personalized treatment, these challenges highlight the need for better data standardization, improved model interpretability, robust external validation, ethical safeguards, and more accessible computational infrastructure before such systems can be fully integrated into routine clinical practice (Osse and Zhou *et al.*, 2026).

Future Directions of Biomarkers of AD

The future of Artificial Intelligence (AI)-based biomarkers in Alzheimer's disease is poised to transform early diagnosis, disease monitoring, and personalized therapeutics. One major direction is the integration of multi-modal data, combining neuroimaging (MRI, PET), fluid biomarkers (amyloid- β , phosphorylated tau), genomics, and digital biomarkers derived from wearable devices. Advanced AI models, particularly deep learning architectures, are expected to improve the sensitivity and specificity of early detection by identifying subtle preclinical changes that are not discernible through conventional analysis. The application of explainable AI (XAI) is also gaining importance to address the "black-box" nature of many machine learning models. Enhancing interpretability will increase clinician trust and facilitate regulatory approval by providing transparent decision-making pathways. This is particularly critical in clinical environments where diagnostic accountability is essential.

Finally, the translation of AI-based biomarkers from research to real-world clinical practice will require robust validation, regulatory approval, and integration into healthcare systems. Future innovations may also include real-time monitoring through digital platforms and mobile health technologies, enabling continuous assessment of cognitive function outside traditional clinical settings (Ben-Jaafar *et al.*, 2026).

CONCLUSION

Alzheimer's disease remains a major global health challenge due to its progressive nature, late clinical diagnosis, and lack of curative treatment. The emergence of Artificial Intelligence (AI) has significantly transformed the field of biomarker research by enabling the integration and analysis of complex, high-dimensional data from neuroimaging, genetics, molecular studies, and digital health sources. AI-driven approaches have demonstrated strong potential in improving early detection, enhancing diagnostic accuracy, and predicting disease progression with greater precision than conventional methods.

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ABBREVIATIONS

AD: Alzheimer's Disease; **AI:** Artificial Intelligence; **ML:** Machine Learning; **DL:** Deep Learning; **MRI:** Magnetic Resonance Imaging; **PET:** Positron Emission Tomography; **CSF:** Cerebrospinal Fluid; **MCI:** Mild Cognitive Impairment; **fMRI:** Functional Magnetic Resonance Imaging; **CNNs:** Convolutional Neural Networks; **RNNs:** Recurrent Neural Networks; **XAI:** Explainable Artificial Intelligence.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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