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# Emerging Biomarkers for Early Detection of Alzheimer's Disease: Progress and Challenges

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**Abstract**

Alzheimer's disease is a neurodegenerative disorder characterized by progressive cognitive decline, which poses a growing global health challenge due to an aging population. Early Diagnosis and intervention are crucial in slowing disease progression and improving patient outcomes. Biomarkers have emerged as pivotal tools in detecting AD at its presymptomatic stages, offering insights into underlying pathophysiological processes before clinical symptoms appear. This review highlights the role of emerging biomarkers, including amyloid-β, Tau, neurofilament light chain, and genetic markers, in early detection, disease monitoring, and personalized treatment strategies. Advances in mass spectrometry, liquid biopsy, and neuroimaging technologies have enhanced biomarker sensitivity, enabling better prediction of disease progression. Despite these advances, challenges remain, including issues with biomarker sensitivity and specificity, the high cost of diagnostic technologies, and ethical concerns about genetic testing and patient privacy. Standardization across assays and platforms is crucial for clinical application. The future of AD biomarker research lies in integrating multiple biomarkers and embracing precision medicine to tailor treatments to individual patient profiles.

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## 1. Introduction

The primary symptoms of Alzheimer's disease (AD), a progressive neurodegenerative illness, are behavioural abnormalities, memory loss, and cognitive decline that substantially hinder day-to-day functioning. About 60–70% of dementia cases are caused by AD, making it the most prevalent cause of dementia. Although early-onset forms can occur in younger people, usually due to genetic mutations, they are most frequently seen in people over 65 [1]. As the world's population ages, the prevalence of AD is rising quickly. According to the World Health Organization, AD is the leading cause of dementia, which is predicted to triple to 152 million people by 2050. According to the Alzheimer's Association, over 6 million Americans currently have AD, and by 2050, that number is expected to increase to almost 13 million [2]. The aging of the world's population and the increasing prevalence of the disease highlight the crucial role of early detection and treatment in its management. For several reasons, it is essential to detect AD early. First of all, it enables the prompt application of therapeutic measures that can reduce symptoms and slow the course of the disease [3].

Additionally, early identification gives people and their families the chance to make plans, such as long-term care, financial, and legal decisions. Additionally, since treatment efficacy is frequently higher in the early stages of AD, the development of medications intended to slow the disease's progression has made early Diagnosis even more important. Furthermore, early detection can shed light on the pathophysiological mechanisms underlying AD, potentially leading to the discovery of biomarkers for Diagnosis, prognosis, and tracking treatment response. Therefore, improving clinical outcomes and expanding our knowledge of AD depend on our ability to identify the disease in its presymptomatic stage [4].

## 2. Challenges in Early Diagnosis

Nowadays, a combination of clinical evaluation, neuroimaging, and cognitive tests is used to diagnose AD. Nevertheless, there isn't a single test that can

accurately identify AD in its early stages. The most popular methods for Diagnosis are as follows [5].

### 2.1 Clinical Assessment and Cognitive Testing

Cognitive tests such as the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) are used to screen for cognitive impairment. These tests evaluate language, attention, memory, and executive function. Since cognitive symptoms often manifest only after significant neurodegeneration, these tools help detect cognitive decline but are not sufficient for early detection [6].

### 2.2 Neuroimaging

The accumulation of amyloid plaques and structural brain alterations characteristic of AD can be detected using neuroimaging methods such as positron emission tomography (PET) and magnetic resonance imaging (MRI). Atrophy in AD-affected brain regions, especially the hippocampus, can be detected by MRI scans [7]. PET scans provide promising information about amyloid deposition, particularly those that detect amyloid-beta plaques (such as Pittsburgh compound B or florbetapir). However, access to these imaging methods may be restricted, and they are costly. Furthermore, even though amyloid plaques are a hallmark of AD, some cognitively normal older adults also have them, making it more difficult to use them as early-stage AD diagnostic markers [8].

### 2.3 Cerebrospinal Fluid Biomarkers

The Diagnosis of AD is also supported by CSF biomarkers, such as tau protein and amyloid-beta (Aβ) levels. Patients with AD often have higher levels of Tau and phosphorylated Tau and lower levels of Aβ42. However, lumbar puncture, an invasive procedure rarely used in clinical practice, is necessary for CSF testing. Furthermore, several variables, such as other neurodegenerative illnesses, may affect how these biomarkers are interpreted [9].

### 2.4 Genetic Testing

Particularly in cases of early-onset AD, genetic testing, specifically for the apolipoprotein E (ApoE) gene, can help identify individuals who are more genetically susceptible to developing AD. Genetic testing does have certain drawbacks, though, such as the inability to accurately predict a person's likelihood of developing AD and the ethical ramifications of genetic testing, which include psychological effects and privacy issues. Additionally, genetic testing for ApoE alone is insufficient for early Diagnosis because the great majority of AD cases occur sporadically [10]. Even with these diagnostic resources, it is still difficult to identify AD in its early stages. The diagnostic process is made more difficult by the overlap of AD with other types of cognitive decline, including vascular dementia and mild cognitive impairment (MCI). The uncertainty is further increased by the inability to distinguish between people who may not develop full-blown dementia and those who will. Because its symptoms, like mild memory loss, are subtle and mimic those of normal aging, early-stage AD is frequently hard to diagnose [11].

### 3.2.2 Protein Biomarkers

An important Part of the pathophysiology of AD involves protein biomarkers. Since the disease is characterized by abnormal protein processing and

## 3. Role of Biomarkers in Early Detection

### 3.1 Biomarkers and Their Significance in AD

Measurable biological indicators, known as biomarkers, can provide important information about the occurrence, course, and prognosis of a disease. Biomarkers for AD are crucial for understanding the cellular and molecular alterations in the brain that occur long before symptoms appear. Biomarkers for early AD detection can be used to track the disease's progression, identify at-risk individuals, and assess how well treatment interventions are working. In AD, biomarkers are crucial for early Diagnosis, disease management, and treatment in several important areas. Since biomarkers can help identify people in the presymptomatic stages of AD, even before significant cognitive decline, early detection is one of their most crucial roles. Early detection is essential for initiating treatments that may delay or reduce the disease's progression [12]. Furthermore, biomarkers are critical for disease monitoring because they enable medical professionals to track the progression of AD over time and assess how well treatment plans are working. By measuring specific biomarkers, healthcare providers can determine how well a patient is responding to therapies and make necessary adjustments. Additionally, biomarkers provide important information about the prognosis of AD, enabling physicians to forecast how the disease will develop in the future, including how quickly mild cognitive impairment (MCI) will give way to dementia. Planning for long-term care and treatment is aided by this prognostic ability. Last but not least, personalized medicine increasingly uses biomarkers to tailor treatment options to each patient's biomarker profile. By focusing on the unique molecular features of the disease in each individual, this method helps optimize treatment approaches and enhances patient outcomes [13].

### 3.2 Types of Biomarkers

#### 3.2.1. Genetic Biomarkers ε4

Certain genetic mutations or variations linked to an elevated risk of AD are known as genetic biomarkers. These markers shed light on the genetic susceptibility to AD, which is crucial for risk assessment and early detection. The Apolipoprotein E gene, which encodes a protein involved in lipid metabolism, is the best-known genetic biomarker for AD. While the ε2 allele of the ApoE gene is thought to be protective, the ε4 allele is linked to an increased risk of developing AD. Two copies of the ApoE ε4 allele increase a person's risk of developing AD, often at an earlier age. However, since many people with the ε4 allele do not develop AD, ApoE testing alone is insufficient for Diagnosis [14]. In rare cases, early-onset AD is caused by mutations in specific genes, such as presenilin-1 (PSEN1), presenilin-2 (PSEN2), and the amyloid precursor protein (APP). These mutations lead to the accumulation of amyloid plaques in the brain and are typically inherited in an autosomal dominant pattern. Genetic testing for these mutations can provide definitive diagnoses in early-onset cases but is not useful for the more common late-onset AD [15].

aggregation, protein biomarkers are useful tools for monitoring and Diagnosis [16]. Amyloid plaques characterize AD. In the brain, amyloid-beta (Aβ) peptides, especially the Aβ42 form, accumulate and form plaques that impair cell function. One of the main markers of AD is a drop in Aβ42 levels in cerebrospinal fluid (CSF) and its deposition in the brain, as shown by positron emission tomography (PET) [17]. Tau is a protein that helps stabilize neurons' microtubules. Tau is hyperphosphorylated in AD and creates twisted tangles inside neurons, which exacerbates neurodegeneration. Measurements of phosphorylated Tau (p-tau) and total Tau (t-tau) in CSF can be useful biomarkers for AD Diagnosis. The development of neurodegeneration and the presence of tau tangles in the brain are associated with elevated CSF levels of these tau proteins [18].

### 3.2.3 Imaging Biomarkers

Structural and functional alterations in the brain caused by AD can be visualized using neuroimaging techniques. These biomarkers aid in the early detection of alterations in memory and cognitive function-related brain regions [19]. Positron emission tomography (PET) can detect amyloid plaques and tau tangles in the brain. PET scans offer fine-grained images of the brain, and the patient may receive an injection of a radiolabelled tracer, such as florbetapir (for amyloid) or flortaucipir (for Tau). PET is an effective tool for early Diagnosis because it can identify the buildup of tau tangles or amyloid plaques even before clinical symptoms manifest [20]. Resonance of Magnetism Imaging (MRI) scans are frequently used to evaluate brain atrophy, especially in regions such as the hippocampus, which are important for memory and cognition. Even though early-stage brain shrinkage might not be apparent, MRI can still detect structural alterations that are linked to the advancement of the disease. Furthermore, brain activity during cognitive tasks is measured using functional magnetic resonance imaging (fMRI), which can also change in AD [21].

Figure 1 shows Amyloid PET scans comparing an Alzheimer's brain and a healthy brain. The Alzheimer's brain shows extensive cortical amyloid deposition (red) and neurofibrillary tangles (blue), indicating abnormal protein accumulation associated with cognitive decline. In contrast, the healthy brain shows no abnormal tracer uptake, reflecting normal protein distribution. This comparison highlights the diagnostic utility of PET imaging in distinguishing Alzheimer's pathology from healthy brain function [22].

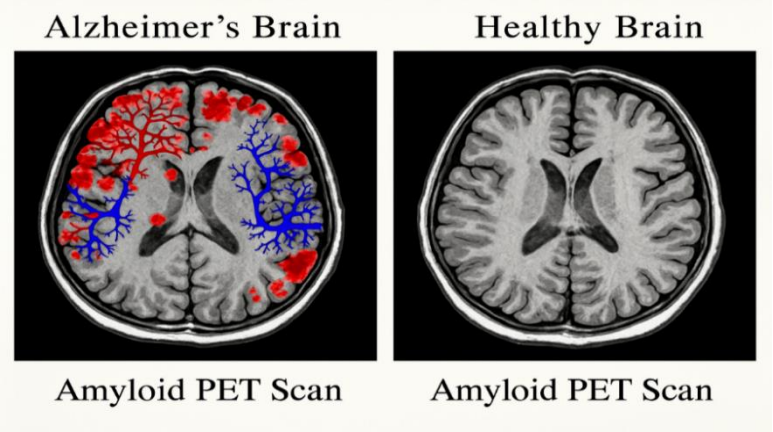


**Figure 1: Represents amyloid PET scans comparing an Alzheimer's brain and a healthy brain.** The Alzheimer's brain shows widespread cortical amyloid deposition (red) and tau neurofibrillary tangles (blue). In contrast, the healthy brain shows no abnormal tracer uptake, indicating the absence of amyloid or tau pathology.

### 3.2.4 Fluid-based Biomarkers

Fluid-based biomarkers are molecules that can indicate changes in the brain and are present in bodily fluids like blood or CSF. Repeatable and non-invasive AD testing may be possible with these biomarkers [23]. CSF One of the best techniques for identifying alterations linked to AD is biomarker analysis. Aβ42, t-tau, and p-tau are important CSF biomarkers. As previously stated, AD is characterized by increased Tau and phosphorylated Tau levels and decreased Aβ42 levels. However, the procedure for obtaining a CSF lumbar puncture is invasive and is not frequently used in clinical settings [24]. The development of blood-based biomarkers for AD has gained significant attention due to their non-invasive nature and potential for widespread use. Biomarkers such as plasma Aβ and NFL are being explored for their diagnostic and prognostic utility. Blood tests that detect specific patterns of proteins associated with AD may help to identify at-risk individuals, monitor disease progression, and assess treatment responses. Recent advances in blood-based biomarkers have shown promise, but they are still in the validation stage [25].

**Table 1** presents the different types of AD biomarkers genetic, protein, imaging, and fluid-based and contrasts them. From early-stage markers such as Tau and amyloid-beta to later-stage markers such as NfL, it describes their clinical significance, disease-stage relevance, and detection techniques. Despite providing insightful information about the course and outcome of diseases, issues with cost, sensitivity, and standardization prevent their widespread use in clinical settings. The potential of these biomarkers to revolutionize AD Diagnosis and treatment is highlighted in the table [26].

**Table 1: Comparison of Biomarker Types in Alzheimer's Disease**

| S. No. | Biomarker Type | Example | Detection Method | Stage of Disease Detection | Clinical Relevance | Reference |
|---|---|---|---|---|---|---|
| 1 | **CSF Biomarkers** | Aβ42, Tau | Lumbar Puncture, ELISA, Mass Spectrometry | Early to moderate stages | Predicts cognitive decline, amyloid, and tau deposition | [27], [28] |
| 2 | **Neuroimaging Biomarkers** | Amyloid PET, FDG-PET | PET Scanning, MRI | Presymptomatic to advanced stages | Visualizes amyloid plaques, key for early Diagnosis | [29] |
| 3 | **Genetic Biomarkers** | APOE ε4 | Genotyping | Presymptomatic | Genetic risk factor for Alzheimer's aids in identifying at-risk individuals | [30] |
| 4 | **Blood Biomarkers** | Plasma Aβ, P-tau | ELISA, Mass Spectrometry, Immunoassays | Early to moderate stages | Non-invasive monitoring of disease progression | [31] |
| 5 | **Proteomics** | Clusterin, BDNF | Mass Spectrometry, Protein Microarrays | All stages | Involvement in neuroinflammation and neuronal survival | [32], [33] |
| 6 | **Metabolic Biomarkers** | Hypermetabolism (via PET) | PET Scanning | Early to moderate stages | Changes in brain metabolism, early signs of cognitive impairment | [34] |
| 7 | **Epigenetic Biomarkers** | DNA Methylation Patterns | Bisulfite Sequencing, PCR | Early to preclinical stages | Alters gene expression, Alzheimer's risk, and pathology | [35] |
| 8 | **MicroRNA Biomarkers** | miR-29, miR-125b | qRT-PCR, NGS | Presymptomatic | Involved in amyloid and tau regulation | [36], [37] |
| 9 | **Exosome Biomarkers** | Aβ, Tau, miRNAs | Nanoparticle Tracking, ELISA | Early stages | Neuroinflammation and protein clearance insights | [38] |
| 10 | **Metabolomic Biomarkers** | Aβ-associated metabolites | Mass Spectrometry, NMR | Early to moderate stages | Changes in the metabolic profile can help identify preclinical Alzheimer's | [39] |
| 11 | **Inflammatory Biomarkers** | Cytokines, CRP | ELISA, Immunoassays | All stages | Inflammatory markers linked to AD | [40] |
| 12 | **Neurodegeneration Biomarkers** | NfL (Neurofilament Light Chain) | Immunoassays, ELISA | All stages | Tracks axonal damage and neuronal loss, useful for disease monitoring | [41] |
| 13 | **Tau Biomarkers** | Total Tau, Phosphorylated Tau | ELISA, Western Blot | Early to advanced stages | Core Alzheimer's biomarkers correlate with cognitive decline and brain atrophy | [42] |
| 14 | **Amyloid Biomarkers** | Amyloid-beta (Aβ) | PET, CSF, Blood Tests | Presymptomatic to early stages | Detects amyloid plaques, pivotal for Diagnosis and therapeutic development | [43] |
| 15 | **Cognitive Biomarkers** | MMSE, MoCA | Neuropsychological Testing | Early to moderate stages | Measures cognitive impairment, useful for therapeutic monitoring | [44] |
| 16 | **Mitochondrial Biomarkers** | Mitochondrial DNA mutations | PCR, NGS | Early to preclinical stages | Linked to mitochondrial dysfunction and Alzheimer’s pathology | [45] |
| 17 | **Neurovascular Biomarkers** | Vascular Amyloid | PET Imaging | Early to late stages | Identifies vascular contributions to Alzheimer’s progression | [46] |
| 18 | **Autophagy Biomarkers** | LC3, Beclin-1 | Western Blot, Immunofluorescence | All stages | Disrupted autophagy in Alzheimer’s, a target for potential therapies | [47] |
| 19 | **Apoptosis Biomarkers** | Caspases, Bcl-2 proteins | ELISA, Flow Cytometry | Advanced stages | Key for understanding cell death pathways and Alzheimer’s progression | [48] |
| 20 | **Gut Microbiota Biomarkers** | Microbial Composition | 16S rRNA Sequencing, Microbial Culturing | Early to preclinical stages | Impacts neurodegeneration via the gut-brain axis | [49] |

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|---|---|---|---|---|---|---|
| 21 | **Hormonal Biomarkers** | Cortisol, Thyroid Hormones | ELISA, Radioimmunoassay | Early to moderate stages | Hormonal changes may influence Alzheimer's development and progression | [50] |
| 22 | **Vascular Biomarkers** | Endothelial Markers | ELISA, Flow Cytometry | Presymptomatic to early stages | Early signs of vascular changes linked to Alzheimer's | [51] |
| 23 | **Angiogenesis Biomarkers** | VEGF | ELISA, Immunohistochemistry | Early to moderate stages | Involved in neurovascular health and disease progression | [52] |
| 24 | **Autophagic Pathway Biomarkers** | Beclin-1, ATG5 | Western Blot, Immunohistochemistry | Early to late stages | Dysregulated autophagic pathways contribute to Alzheimer's pathology | [53] |
| 25 | **Cholinergic Biomarkers** | AChE | Biochemical Assays, Immunoassays | Early to advanced stages | Involvement in cholinergic dysfunction in AD | [54] |
| 26 | **Oxidative Stress Biomarkers** | MDA, 8-OHdG | ELISA, HPLC | Early to advanced stages | Reflects oxidative damage, linked to Alzheimer's pathology | [55] |
| 27 | **Serum Biomarkers** | Serum BDNF | ELISA | Early to moderate stages | Correlates with cognitive decline, neuronal growth, and repair | [56], [57] |
| 28 | **Neurovascular Coupling Biomarkers** | fMRI | MRI | Early to preclinical stages | Measures cerebral blood flow, related to Alzheimer's risk and neuronal activity | [58] |
| 29 | **Postmortem Brain Biomarkers** | Neurofibrillary Tangles, Amyloid Plaques | Histopathology, Immunohistochemistry | End-stage | Provides definitive Diagnosis and links pathology to clinical progression | [59] |
| 30 | **Cardiovascular Biomarkers** | Homocysteine, Lipids | Blood Tests | All stages | Elevated cardiovascular risk correlates with Alzheimer's and aids in assessing comorbidities. | [60] |

## 4. Advances in Biomarker Technologies

### 4.1 Technological Improvements in Detection

#### 4.1.1 Mass Spectrometry (MS)

By enabling high-resolution, high-throughput, and quantitative profiling of complex biological samples, recent advances in mass spectrometry have fundamentally changed the process of identifying and validating biomarkers. Low-abundance proteins, metabolites, and lipids that were previously undetectable can now be detected thanks to the remarkable sensitivity of contemporary MS platforms like MALDI-TOF, LC-MS/MS, and Orbitrap. These systems are now capable of analyzing protein isoforms and post-translational modifications, providing vital insights into the mechanisms underlying disease. By combining MS with bioinformatics pipelines, data interpretation is further improved and new biomarkers for precision medicine are found [61].

#### 4.1.2 Immunoassays

Additionally, immunoassay technology has changed dramatically, moving from traditional enzyme-linked immunosorbent assays (ELISAs) to multiplexed, automated, and ultrasensitive platforms like digital immunoassays and electrochemiluminescence. These sophisticated systems offer greater specificity and reproducibility when quantifying multiple biomarkers simultaneously. Large-scale population screening and point-of-care testing are enabled by innovations such as nanobody-based sensors and microfluidic immunoassays, which have reduced assay times and sample volumes. These improvements improve diagnostic precision, especially in therapeutic monitoring and early disease detection [62].

### 4.2 Liquid Biopsy

Liquid biopsy represents one of the most transformative developments in biomarker technology. It involves the non-invasive analysis of circulating biomarkers such as cell-free DNA (cfDNA), circulating tumor cells (CTCs), microRNAs, and extracellular vesicles present in blood or other body fluids. These biomarkers provide real-time insights into pathological changes without the need for invasive tissue sampling. Advances in next-generation sequencing (NGS) and digital PCR have increased the sensitivity and specificity of detecting minimal residual disease and early-stage cancers. Beyond oncology, liquid biopsy applications are expanding to neurodegenerative and cardiovascular disorders, making it a cornerstone for predictive and preventive healthcare [63].

## 5. Challenges in Using Emerging Biomarkers

**5.1 Sensitivity and Specificity Issues**Even with significant technological advancements, the diagnostic accuracy of many new biomarker assays remains limited. Subtle biological overlap between neurodegenerative conditions frequently results in false positives (biomarkers elevated but not caused by AD) and false negatives (pathology present but biomarkers undetected) in research on AD. For example, tau assays may show

non-specific elevations in other tauopathies, and peripheral metabolism may affect plasma Aβ42/Aβ40 ratios. One of the main challenges in transferring biomarkers from research to routine clinical use is maintaining both high sensitivity (identifying actual disease cases) and high specificity (preventing misclassification) [64].

### 5.2 Ethical and Social Implications

Significant ethical and social issues arise from the growing use of genomic and molecular biomarkers, particularly regarding genetic testing, privacy, and data sharing. Individuals and families may face psychological, social, and insurance-related ramifications if genetic risk profiling, such as polygenic risk scoring or APOE genotyping, reveals predispositions to AD long before symptoms manifest. Furthermore, worries about data privacy, informed consent, and fair access become critical as biomarker data is kept in digital biobanks and cloud platforms. Therefore, ethical frameworks are required to strike a balance between patient autonomy, scientific advancement, and public trust [65].

### 5.3 Standardization of Biomarker Assays

Another major barrier to biomarker implementation is the lack of assay standardization across laboratories and analytical platforms. Differences in sample handling, reagent quality, calibration procedures, and reporting units hinder reproducibility and inter-laboratory comparability. This variability complicates meta-analyses and cross-cohort validation studies, delaying regulatory approval. To address these challenges, global initiatives such as the Alzheimer's Association Global Biomarker Standardization Consortium (GBSC) and the International Federation of Clinical Chemistry (IFCC) are working to establish harmonized reference materials, standardized protocols, and quality assurance programs [66].

## 6. Clinical Implications

Biomarkers are becoming an integral component in the early detection of AD, particularly in presymptomatic stages. Early Diagnosis can allow for timely interventions, potentially altering the course of the disease. Several biomarkers, such as amyloid-β and tau proteins, have shown promise in detecting AD-related pathology before cognitive decline becomes clinically evident. In particular, plasma Aβ and tau PET imaging provides a window into the brain's pathological processes, which may precede symptoms by several years [67]. This presymptomatic detection has the potential to transform clinical care by facilitating early treatment — when therapies are most likely to be effective —and improving clinical trial recruitment. In addition to aiding early Diagnosis, biomarkers are critical in monitoring disease progression in AD. The predictive value of biomarkers such as neurofilament light chain (NfL), CSF tau, and synaptic proteins correlates strongly with disease stage and cognitive decline. These biomarkers can track neuronal injury, tau-related neurodegeneration, and synaptic dysfunction over time, providing valuable insight into the rate of progression and response to treatment. Regular biomarker testing could also aid in stratifying patients in clinical trials and assist clinicians in personalizing treatment regimens based on disease severity and progression rate [68].

Figure 2 shows a schematic representation of integrating imaging techniques and deep learning methods for early Diagnosis and monitoring of AD. MRI and PET imaging provide structural and molecular information, while advanced deep learning models such as CNNs, RNNs, and Transformers analyze complex data patterns to enhance predictive modelling. This multimodal approach enables differentiation between mild cognitive impairment, early Alzheimer's, and advanced stages, improving early detection and disease progression monitoring [69].

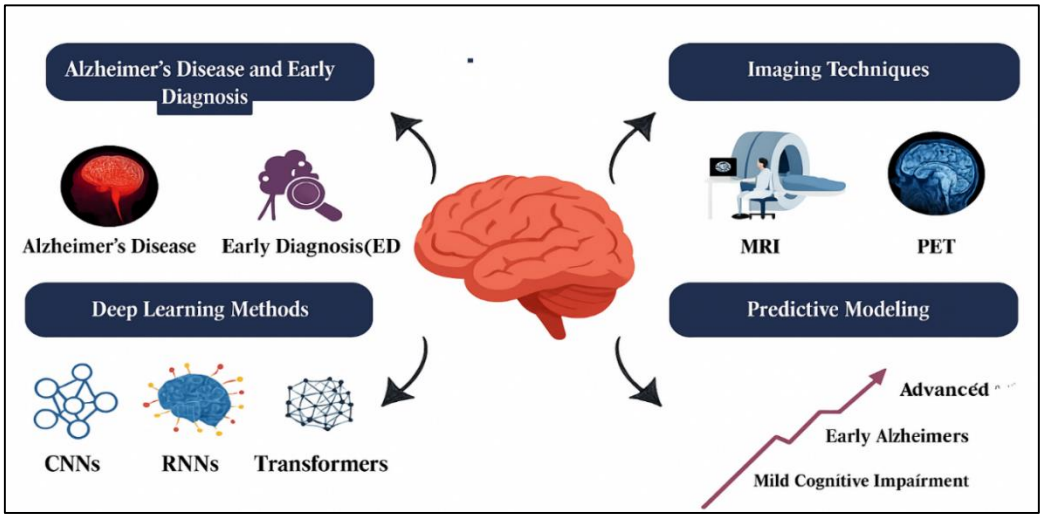


**Figure 2:** Integration of multimodal biomarkers for early detection and monitoring of AD, illustrating the combined use of genetic, protein, imaging, and fluid-based indicators. Genetic markers provide insights into hereditary risk, protein biomarkers such as amyloid and Tau reflect pathological changes, imaging techniques, including MRI and PET, visualize structural and molecular alterations, and fluid-based biomarkers from cerebrospinal fluid and blood offer accessible measures of disease progression.

## 7. Future Directions

The future of AD biomarker use lies in integrating multiple biomarkers to improve diagnostic accuracy and predictive power. Combining biomarkers from various platforms such as CSF (for Tau and Aβ), plasma (for neurofilament light chain and Tau), and imaging modalities (such as PET and MRI) holds promise for developing multimodal diagnostic criteria. Multi-biomarker approaches could potentially identify individuals at the highest risk of progression, distinguishing AD from other dementias, and enabling tailored therapeutic strategies. As the field moves towards precision medicine, personalized medicine will become increasingly important in AD Diagnosis and treatment. This approach will rely heavily on biomarkers to define AD subtypes, while accounting for genetic, environmental, and clinical factors. A personalized approach could help identify the most appropriate treatments for different patient profiles, including those based on genetic markers, such as the APOE genotype, or proteomic signatures [70]. Furthermore, it could support individualized care plans, optimizing quality of life for patients in various stages of the disease. Despite these exciting prospects, several challenges remain in the clinical implementation of biomarkers. The high cost of advanced technologies such as PET imaging and mass spectrometry, along with their limited availability in certain regions, limits widespread clinical adoption. Moreover, issues with standardization**,** data interpretation**,** and assay reproducibility still need to be addressed. Furthermore, the ethical and social implications surrounding genetic testing and patient data privacy continue to complicate the practical use of biomarkers in clinical settings [71].

## Conclusion

This review emphasizes the transformative role of biomarkers in the early detection and monitoring of AD. While significant progress has been made with biomarkers such as amyloid-β, Tau, and NfL, their clinical implementation is still hindered by challenges in sensitivity, specificity, and standardization across platforms. Genetic and protein biomarkers provide invaluable insights into disease mechanisms and can guide personalized treatment plans, but ethical concerns about genetic testing and data privacy remain pressing issues. As we move toward multi-biomarker approaches and precision medicine, overcoming these barriers will be crucial in enhancing the clinical application of biomarkers. Future research must focus on improving assay reproducibility, reducing costs, and establishing standardized protocols to enable broader access and reliability in clinical settings. With ongoing advancements, biomarkers have the potential to revolutionize the way AD is diagnosed and managed, paving the way for more effective treatments and better patient outcomes. This explores the role of emerging biomarkers in the early detection and monitoring of AD. Biomarkers such as amyloid-β, tau proteins, and NfL offer insights into disease progression and facilitate presymptomatic Diagnosis. Advances in technologies like mass spectrometry and neuroimaging have improved detection sensitivity. However, challenges remain in sensitivity, specificity, cost, and ethical concerns, particularly regarding genetic testing. The future lies in integrating multiple biomarkers for more accurate predictions and personalized treatment approaches. Overcoming these challenges is essential for effective clinical implementation.

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## Author Contribution

**PC;** Data Analysis and interpretation, **TS;** Data collection, **AS;** Writing the paper.

## Conflict of Interest

The authors declare no conflict of interest.

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## Reference

1. C. R. Jack et al., “Introduction to the recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease,” Alzheimer’s Dement., 2011, doi: 10.1016/j.jalz.2011.03.004.
2. M. R. Khan, D. Kumar, S. Shamim, K. Sunand, S. Sharma, and G. Rawat, “Ethnopharmacological relevance of Citrus limon (L.) Burm. f. as adjuvant therapy,” Ann. Phytomedicine An Int. J., vol. 12, no. 2, pp. 169–179, 2023, doi: 10.54085/ap.2023.12.2.19.
3. P. Mirzayi, P. Shobeiri, A. Kalantari, G. Perry, and N. Rezaei, “Optogenetics: implications for Alzheimer’s disease research and therapy,” 2022. doi: 10.1186/s13041-022-00905-y.
4. D. H. O’Day, “Alzheimer’s Disease: A short introduction to the calmodulin hypothesis,” 2019. doi: 10.3934/Neuroscience.2019.4.231.
5. M. Pais et al., “Early diagnosis and treatment of Alzheimer’s disease: New definitions and challenges,” Brazilian J. Psychiatry, 2020, doi: 10.1590/1516-4446-2019-0735.
6. J. Jia et al., “Biomarker Changes during 20 Years Preceding Alzheimer’s Disease,” N. Engl. J. Med., 2024, doi: 10.1056/nejmoa2310168.
7. F. Márquez and M. A. Yassa, “Neuroimaging Biomarkers for Alzheimer’s Disease,” 2019. doi: 10.1186/s13024-019-0325-5.
8. E. Lin, C. H. Lin, and H. Y. Lane, “Deep learning with neuroimaging and genomics in alzheimer’s disease,” 2021. doi: 10.3390/ijms22157911.
9. D. A. McGrowder et al., “Cerebrospinal fluid biomarkers of alzheimer’s disease: Current evidence

and future perspectives," 2021. doi: 10.3390/brainsci11020215.
10. Y. A. Reyes-Domínguez, L. E. Figuera, and A. J. L. Brambila-Tapia, "Perceptions of Knowledge, Disease Impact and Predictive Genetic Testing in Family Members at Risk to Develop Early-Onset Alzheimer's Disease (EOAD) and Their Levels of Suicidal Ideation: A Mixed Study," Brain Sci., 2023, doi: 10.3390/brainsci13030501.
11. M. Bocchetta et al., "Genetic Counseling and Testing for Alzheimer's Disease and Frontotemporal Lobar Degeneration: An Italian Consensus Protocol," J. Alzheimer's Dis., 2016, doi: 10.3233/JAD-150849.
12. B. Arslan, H. Zetterberg, and N. J. Ashton, "Blood-based biomarkers in Alzheimer's disease – moving towards a new era of diagnostics," Clin. Chem. Lab. Med., 2024, doi: 10.1515/cclm-2023-1434.
13. T. Bieber et al., "Clinical phenotypes and endophenotypes of atopic dermatitis: Where are we, and where should we go?," 2017. doi: 10.1016/j.jaci.2017.01.008.
14. J. L. Ebenau et al., "Risk of dementia in APOE ε4 carriers is mitigated by a polygenic risk score," Alzheimer's Dement. Diagnosis, Assess. Dis. Monit., 2021, doi: 10.1002/dad2.12229.
15. Y. Wang et al., "Associations of circulating C-reactive proteins, APOE ε4, and brain markers for Alzheimer's disease in healthy samples across the lifespan," Brain. Behav. Immun., 2022, doi: 10.1016/j.bbi.2021.12.008.
16. R. Kehm, T. Baldensperger, J. Raupbach, and A. Höhn, "Protein oxidation - Formation mechanisms, detection and relevance as biomarkers in human diseases," 2021. doi: 10.1016/j.redox.2021.101901.
17. C. R. Jack et al., "Predicting amyloid PET and tau PET stages with plasma biomarkers," Brain, 2023, doi: 10.1093/brain/awad042.
18. C. Maschio and R. Ni, "Amyloid and Tau Positron Emission Tomography Imaging in Alzheimer's Disease and Other Tauopathies," 2022. doi: 10.3389/fnagi.2022.838034.
19. S. Pai et al., "Foundation model for cancer imaging biomarkers," Nat. Mach. Intell., 2024, doi: 10.1038/s42256-024-00807-9.
20. I. Dregely, D. Prezzi, C. Kelly-Morland, E. Roccia, R. Neji, and V. Goh, "Imaging biomarkers in oncology: Basics and application to MRI," J. Magn. Reson. Imaging, 2018, doi: 10.1002/jmri.26058.
21. F. Y. Chiu and Y. Yen, "Imaging biomarkers for clinical applications in neuro-oncology: current status and future perspectives," 2023. doi: 10.1186/s40364-023-00476-7.
22. J. Penney, W. T. Ralvenius, and L. H. Tsai, "Modeling Alzheimer's disease with iPSC-derived brain cells," 2020. doi: 10.1038/s41380-019-0468-3.
23. H. Zetterberg and K. Blennow, "Moving fluid biomarkers for Alzheimer's disease from research tools to routine clinical diagnostics," 2021. doi: 10.1186/s13024-021-00430-x.
24. H. Zetterberg and B. B. Bendlin, "Biomarkers for Alzheimer's disease—preparing for a new era of disease-modifying therapies," 2021. doi: 10.1038/s41380-020-0721-9.
25. A. Leuzy, N. Mattsson-Carlgren, S. Palmqvist, S. Janelidze, J. L. Dage, and O. Hansson, "Blood-based biomarkers for Alzheimer's disease," EMBO Mol. Med., 2022, doi: 10.15252/emmm.202114408.
26. H. Zetterberg and S. C. Burnham, "Blood-based molecular biomarkers for Alzheimer's disease," 2019. doi: 10.1186/s13041-019-0448-1.
27. K. Blennow, "Diagnostic and theragnostic cerebrospinal fluid biomarkers for Alzheimer's disease," Clin. Chem. Lab. Med., 2014.
28. S. A. Ali, S. Ali, S. Rastogi, B. Shivhare, and M. Muztaba, "A Comprehensive Review on Advancements in Nanocarriers-Based Peptide Delivery for Cancer Therapeutics," Micro Nanosyst., vol. 17, no. 4, pp. 283–297, 2025, doi: 10.2174/0118764029358553250325040749.
29. B. Schmand, P. Eikelenboom, and W. A. Van Gool, "Value of diagnostic tests to predict conversion to alzheimer's disease in young and old patients with amnestic mild cognitive impairment," J. Alzheimer's Dis., 2012, doi: 10.3233/JAD-2012-111703.
30. I. Skoog et al., "A non-APOEPolygenic risk score foralzheimer's disease is associated with cerebrospinal fluid neurofilament light in a representative sample of cognitively unimpaired 70-year olds," Journals Gerontol. - Ser. A Biol. Sci. Med. Sci., 2021, doi: 10.1093/gerona/glab030.
31. L. Dayon et al., "Plasma Proteomic Profiles of Cerebrospinal Fluid-Defined Alzheimer's Disease Pathology in Older Adults," J. Alzheimer's Dis., 2017, doi: 10.3233/JAD-170426.
32. S. R. Shuken, "An Introduction to Mass Spectrometry-Based Proteomics," J. Proteome Res., 2023, doi: 10.1021/acs.jproteome.2c00838.
33. K. Singh et al., "Deciphering the Genetic Landscape: Exploring the Relationship Between HLA-DQA1, HLA-DQB1, and HLA-DRB1 Genes in Diabetes Mellitus," Curr. Pharmacogenomics Person. Med., vol. 21, pp. 1–11, 2024, doi: 10.2174/0118756921310081240821065036.
34. "Abstracts of the 17th International Symposium on Bioluminescence and Chemiluminescence - (ISBC 2012)," Luminescence, 2012, doi: 10.1002/bio.2341.
35. C. Villa and A. Stoccoro, "Epigenetic Peripheral Biomarkers for Early Diagnosis of Alzheimer's Disease," 2022. doi: 10.3390/genes13081308.
36. C. Eyileten et al., "Expression of miR-223 to predict outcomes after transcatheter aortic valve implantation," Cardiol. J., 2024, doi: 10.5603/CJ.a2022.0090.
37. T. Ali, "Chromatography and Spectroscopic Characterization of Nano-Carrier Pharmaceuticals," Pharm. Nanotechnol., 2024, doi: 10.2174/0122117385319695240911115239.
38. S. Li et al., "MicroRNA-128 suppresses tau phosphorylation and reduces amyloid-beta accumulation by inhibiting the expression of GSK3β, APPBP2, and mTOR in Alzheimer's disease," CNS Neurosci. Ther., 2023, doi: 10.1111/cns.14143.
39. P. Chatterjee et al., "Plasma metabolites associated with biomarker evidence of neurodegeneration in cognitively normal older adults," J. Neurochem., 2021, doi: 10.1111/jnc.15128.
40. F. Tas et al., "Serum levels of leptin and proinflammatory cytokines in advanced-stage non-small cell lung cancer," Med. Oncol., 2005, doi: 10.1385/MO:22:4:353.
41. J. Kuhle et al., "A comparative study of CSF neurofilament light and heavy chain protein in MS,"

Mult. Scler. J., 2013, doi: 10.1177/1352458513482374.
42. C. Wattmo, K. Blennow, and O. Hansson, “Cerebrospinal fluid biomarker levels: Phosphorylated tau (T) and total tau (N) as markers for rate of progression in Alzheimer’s disease,” BMC Neurol., 2020, doi: 10.1186/s12883-019-1591-0.
43. N. J. Ashton et al., “Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology,” JAMA Neurol., 2024, doi: 10.1001/jamaneurol.2023.5319.
44. N. Swerdlow et al., “Using an acute drug challenge to predict memantine therapeutic effects in alzheimer’s disease: A preliminary proof of concept and feasibility,” Neuropsychopharmacology, 2020.
45. Y. Liu et al., “NGS-based accurate and efficient detection of circulating cell-free mitochondrial DNA in cancer patients,” Mol. Ther. Nucleic Acids, 2021, doi: 10.1016/j.omtn.2020.12.017.
46. J. Hua et al., “Increased cerebral blood volume in small arterial vessels is a correlate of amyloid-β–related cognitive decline,” Neurobiol. Aging, 2019, doi: 10.1016/j.neurobiolaging.2019.01.001.
47. K. Feng, H. Chen, and C. Xu, “Chondro-protective effects of celastrol on osteoarthritis through autophagy activation and NF-κB signaling pathway inhibition,” Inflamm. Res., 2020, doi: 10.1007/s00011-020-01327-z.
48. J. Sun, S. Wei, Y. Zhang, and J. Li, “Protective Effects of Astragalus Polysaccharide on Sepsis-Induced Acute Kidney Injury,” Anal. Cell. Pathol., 2021, doi: 10.1155/2021/7178253.
49. K. S. Swanson et al., “Effect of fructans, prebiotics and fibres on the human gut microbiome assessed by 16S rRNA-based approaches: A review,” 2020. doi: 10.3920/BM2019.0082.
50. K. D. Wright, R. Hickman, and M. L. Laudenslager, “Hair cortisol analysis: A promising biomarker of HPA activation in older adults,” Gerontologist, 2015, doi: 10.1093/geront/gnu174.
51. [51]M. Philippova et al., “T-cadherin is present on endothelial microparticles and is elevated in plasma in early atherosclerosis,” Eur. Heart J., 2011, doi: 10.1093/eurheartj/ehq206.
52. C. L. Roland, K. D. Lynn, J. E. Toombs, S. P. Dineen, D. G. Udugamasooriya, and R. A. Brekken, “Cytokine levels correlate with immune cell infiltration after anti-VEGF therapy in preclinical mouse models of breast cancer,” PLoS One, 2009, doi: 10.1371/journal.pone.0007669.
53. C. C. Yang, S. P. Hsu, K. H. Chen, and C. T. Chien, “Effect of adenoviral catalase gene transfer on renal ischemia/reperfusion injury in rats,” Chin. J. Physiol., 2015, doi: 10.4077/CJP.2015.BAD324.
54. T. A. Olasehinde and A. O. Olaniran, “Neurotoxicity of anthracene and benz[a]anthracene involves oxidative stress-induced neuronal damage, cholinergic dysfunction and disruption of monoaminergic and purinergic enzymes,” Toxicol. Res., 2022, doi: 10.1007/s43188-021-00115-z.
55. A. A. J. Verlaet et al., “Oxidative stress and immune aberrancies in attention-deficit/hyperactivity disorder (ADHD): a case–control comparison,” Eur. Child Adolesc. Psychiatry, 2019, doi: 10.1007/s00787-018-1239-4.
56. Y. Mori et al., “Serum BDNF as a Potential Biomarker of Alzheimer’s Disease: Verification Through Assessment of Serum, Cerebrospinal Fluid, and Medial Temporal Lobe Atrophy,” Front. Neurol., 2021, doi: 10.3389/fneur.2021.653267.
57. A. K. Jaiswal et al., “Multi-targeted therapeutic exploration of Tamarix gallica flowers for anti-ulcer activity and associated complications,” J. Ayurveda Integr. Med., vol. 15, no. 4, p. 100947, 2024, doi: 10.1016/j.jaim.2024.100947.
58. R. González et al., “Estimation of the density of veins from susceptibility-weighted imaging by using Mamdani fuzzy-type rule-based system. Investigating the neurovascular coupling in migraine,” NeuroImage Clin., 2023, doi: 10.1016/j.nicl.2023.103489.
59. J. A. Trejo-Lopez, A. T. Yachnis, and S. Prokop, “Neuropathology of Alzheimer’s Disease,” 2022. doi: 10.1007/s13311-021-01146-y.
60. A. Waśkiewicz and E. Sygnowska, “Alcohol intake and cardiovascular risk factor profile in men participating in the WOBASZ study,” Kardiol. Pol., 2013, doi: 10.5603/KP.2013.0063.
61. [61]A. N. Neagu, M. Jayathirtha, E. Baxter, M. Donnelly, B. A. Petre, and C. C. Darie, “Applications of Tandem Mass Spectrometry (MS/MS) in Protein Analysis for Biomedical Research,” 2022. doi: 10.3390/molecules27082411.
62. S. Ahmed et al., “Current advances in immunoassays for the detection of antibiotics residues: a review,” 2020. doi: 10.1080/09540105.2019.1707171.
63. H. Gaitsch, R. J. M. Franklin, and D. S. Reich, “Cell-free DNA-based liquid biopsies in neurology,” 2023. doi: 10.1093/brain/awac438.
64. M. X. Fu, P. Simmonds, M. Andersson, and H. Harvala, “Biomarkers of transfusion transmitted occult hepatitis B virus infection: Where are we and what next?,” 2024. doi: 10.1002/rmv.2525.
65. F. Ursin, C. Timmermann, and F. Steger, “Ethical implications of alzheimer’s disease prediction in asymptomatic individuals through artificial intelligence,” Diagnostics, 2021, doi: 10.3390/diagnostics11030440.
66. K. Blennow and H. Zetterberg, “Biomarkers for Alzheimer’s disease: current status and prospects for the future,” 2018. doi: 10.1111/joim.12816.
67. S. Li, C. Wang, W. Wang, and J. Tan, “Trait anxiety, a personality risk factor associated with Alzheimer’s Disease,” 2021. doi: 10.1016/j.pnpbp.2020.110124.
68. A. Nordberg, “Molecular imaging in Alzheimer’s disease: New perspectives on biomarkers for early diagnosis and drug development,” 2011. doi: 10.1186/alzrt96.
69. Z. Zou, C. Liu, C. Che, and H. Huang, “Clinical genetics of Alzheimer’s disease,” 2014. doi: 10.1155/2014/291862.
70. W. Cao and H. Zheng, “Peripheral immune system in aging and Alzheimer’s disease,” 2018. doi: 10.1186/s13024-018-0284-2.
71. D. Walker and L.-F. Lue, “Anti-inflammatory and Immune Therapy for Alzheimers Disease: Current Status and Future Directions,” Curr. Neuropharmacol., 2007, doi: 10.2174/157015907782793667.