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# Modern Biomarkers as Key Tools in the Early Diagnosis and Monitoring of Alzheimer's Disease Progression

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**Abstract**

Advances in the understanding of Alzheimer's disease (AD) pathophysiology, along with the development of neuroimaging and biomarker analysis, have enabled the detection of neurodegenerative changes even before clinical symptoms appear. This article explores the evolution of AD diagnostic criteria, with a particular focus on the pivotal role of cerebrospinal fluid biomarkers (Aβ42, t-tau, p-tau) and brain imaging techniques (MRI, PET). The A/T/N classification system and the concept of compensatory brain mechanisms are also discussed, emphasizing their relevance in early disease detection. The modern diagnostic approach, introduced by the Dubois criteria and further developed by the NIA-AA framework, allows for the identification of AD in its preclinical phase. The presence of biomarker abnormalities in asymptomatic individuals suggests a long latent period and the activation of neuroplastic compensatory processes that may delay symptom onset. The integration of biomarkers has significantly improved diagnostic accuracy, enhanced clinical trial participant selection, and enabled more precise disease monitoring. Despite these advances, effective treatments to halt or reverse disease progression remain elusive, highlighting the urgent need for further research into compensatory mechanisms, individual variability, and early therapeutic strategies.

**Keywords:** Alzheimer's disease, biomarkers, cerebrospinal fluid, neuroimaging, Aβ42, tau protein, A/T/N classification, early diagnosis

## Introduction

Alzheimer's disease is the leading cause of dementia and is rapidly becoming one of the most economically burdensome, fatal, and care-intensive diseases of the 21st century. [1] The initial symptoms of Alzheimer's disease typically involve mild memory difficulties, which gradually worsen, leading to a decline in cognitive functions, challenges in performing complex daily tasks, and impairments across various intellectual abilities. [2] By the time Alzheimer's disease is clinically diagnosed, extensive neuronal loss and advanced neuropathological changes have already occurred in many areas of the brain. [3] Early administration of neuroprotective drugs—before the disease progresses to the mildly symptomatic stage—plays a crucial role in preventing potential damage. [3] To achieve this goal, it is essential to improve

methods for identifying individuals in the early stages of the disease, who exhibit only subtle symptoms before the onset of dementia. [4] Several diagnostic criteria have already been published, based on imaging techniques and cerebrospinal fluid biomarkers, aiming to establish a multifactorial classification of Alzheimer's disease. [5]

## Classical Diagnostic Criteria

Diagnosing Alzheimer's disease has been a significant challenge since its first description by Alois Alzheimer in the early 20th century. [6] By the late 20th century, the first formal diagnostic criteria for Alzheimer's disease were developed by the National Institute of Neurological and Communicative Disorders and Stroke in collaboration with the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). [7] Additionally, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), developed by the American Psychiatric Association, contributed to the standardization of Alzheimer's disease diagnostic criteria. [8]

The NINCDS-ADRDA and DSM-IV criteria define Alzheimer's disease as a clinical syndrome, with three levels of diagnostic certainty: probable, possible, and definite AD. Definitive confirmation—definite AD—typically requires post-mortem histopathological verification to achieve full diagnostic certainty. The sensitivity of these diagnostic criteria ranged from 65% to 96%, reflecting variable effectiveness in identifying the disease. [8,9,10,11] Specificity ranged between 23% and 88% [10,11], as other types of dementia—such as Lewy body dementia, frontotemporal dementia, and vascular dementia—could not be entirely excluded. This limited specificity hindered the precise differentiation of Alzheimer's disease from other neurodegenerative disorders. [10,12]

## Integration of Biomarkers into Diagnostic Criteria

With advancing knowledge of the pathophysiological, molecular, and structural changes involved in Alzheimer's disease, Dubois and colleagues developed new diagnostic criteria that incorporate advanced imaging techniques and cerebrospinal fluid biomarkers. This development has significantly contributed to more accurate identification of the disease at its early stages. [12]

Dubois and collaborators revised the classical diagnostic criteria for Alzheimer's disease by proposing a novel diagnostic framework aimed at detecting the disease before the

onset of full-blown dementia. The new criteria defined a specific clinical phenotype of AD, moving away from the earlier exclusion-based diagnostic approach. This shift addressed the issue of low diagnostic specificity and opened the door to earlier therapeutic interventions that may slow disease progression. [12]

The main criterion proposed by Dubois et al. is episodic memory impairment, which is one of the earliest symptoms appearing in the initial stages of Alzheimer's disease (Criterion A, see Table 1). In addition, they introduced a set of innovative supporting criteria based on biomarkers (Criteria B, C, D, and E), which serve as valuable diagnostic aids. Therefore, the presence of the core criterion—episodic memory impairment—along with at least one biomarker-based criterion, strongly suggests the presence of Alzheimer's-specific pathology.

Table 1. Core Proposed Diagnostic Criteria for Alzheimer's Disease (AD) According to Dubois et al. (2007) [12]

| Criteria | Options |
|---|---|
| Main Criteria for AD Diagnosis (Obligatory) | (A) Early episodic memory failure represented by a gradual or progressive memory dysfunction at the beginning of the disease, informed by the patient or family, lasting more than six months.<br>Associated with objective evidence of significant decline in episodic memory through tests (deferred memory). |
| Support Criteria for AD Diagnosis (At least one present) | (B) Loss of volume of the hippocampus, entorhinal cortex, amygdala or other mesial-temporal structures, evidenced by magnetic resonance imaging (MRI). |
| | (C) Abnormality in CSF biomarkers such as<br>- Low concentrations of Aβ;<br>- Increased t-tau or p-tau concentrations; or<br>- A combination of the three. |
| | (D) Specific metabolic pattern evidenced by PET such as hypometabolism of glucose in bilateral temporal parietal regions. |
| | (E) Autosomal dominant family genetic mutations<br>On chromosomes 21 (APP), 14 (PS1), or 1 (PS2). |

Thanks to the new criteria introduced by Dubois and colleagues [12], earlier and more accurate diagnosis of Alzheimer's disease became possible compared to the previous NINCDS-ADRDA criteria. The new approach encompasses both the earliest stages of the disease—when full-blown dementia has not yet developed—as well as the later stages, in which patients are already experiencing significant functional deficits.

What makes these criteria innovative is that, for the first time, they include biological biomarkers as a key diagnostic component. These biomarkers consist of structural and molecular brain imaging, analysis of biomarkers in cerebrospinal fluid (CSF), and the examination of genetic mutations, all of which contribute to a more objective and reliable diagnosis of Alzheimer's disease. [12]

Following the pioneering inclusion of biomarkers by Dubois and his team, the National Institute on Aging (NIA) and the Alzheimer's Association (AA) developed new diagnostic guidelines in 2011. These guidelines divided Alzheimer's disease into three clinical stages, with each stage having its own diagnostic framework.

The first of these stages is the preclinical phase, during which pathological changes occur in the brain that may progress for up to a decade before the appearance of clinical symptoms. At this stage, changes in cerebrospinal fluid (CSF) biomarkers and brain imaging can already be detected; however, it is still not possible to predict with certainty which individuals will eventually develop dementia. [13]

The second stage is mild cognitive impairment (MCI), characterized by memory disturbances that exceed what is expected for an individual's age and level of education. However, at this stage, these deficits do not significantly impair the person's daily independence. MCI may or may not progress to full-blown Alzheimer's dementia, making early diagnosis and ongoing biomarker monitoring essential for predicting the disease's future course. [14]

The final stage is Alzheimer's dementia, where symptoms have progressed to the point that they significantly interfere with everyday functioning and result in a loss of independence. At this stage, patients experience severe cognitive deficits, affecting not only memory but also reasoning, orientation, communication, and the ability to perform basic daily activities. [15]
The recognition of the preclinical stage, which can develop many years before symptom onset, has made biomarkers a key element of the diagnostic process. Their importance has grown considerably, as they allow for the early detection of pathological brain changes before clinical symptoms appear—opening new opportunities for earlier therapeutic intervention.

## Alzheimer's Disease Biomarkers

Biomarkers are defined as physiological, biochemical, or anatomical indicators that can be measured in vivo and reflect specific pathological changes associated with a disease. In the context of Alzheimer's disease (AD), biomarkers can be classified into two main categories based on the method of analysis: biochemical biomarkers found in cerebrospinal fluid (CSF) and biomarkers obtained through brain imaging techniques. [16,17]

## Cerebrospinal Fluid (CSF) Biomarkers

Cerebrospinal fluid (CSF) biomarkers are now commonly used in everyday clinical practice as a tool to support the diagnosis of mild cognitive impairment (MCI) and Alzheimer's disease (AD). Their use allows for more accurate identification of the disease, particularly in its early stages—before the appearance of advanced clinical symptoms. [18,19,20]

The levels of beta-amyloid peptide (Aβ), total tau (t-tau), and phosphorylated tau (p-tau) in CSF serve as specific biomarkers for Alzheimer's disease. These biomarkers reflect key pathological processes associated with AD, such as Aβ42 aggregation and tau protein hyperphosphorylation, which contribute to neurodegeneration. Because of their high diagnostic value, these markers have been incorporated as supportive indicators of probable Alzheimer's disease in modern diagnostic criteria. [12]

**Aβ42 and Tau as Biomarkers**

There is an inverse correlation between amyloid accumulation in the brain and Aβ42 levels in the cerebrospinal fluid (CSF). In patients with Alzheimer's disease (AD), CSF Aβ42 concentrations are significantly lower compared to healthy individuals. CSF Aβ levels reflect the pathological aggregation of this peptide into amyloid plaques, which reduces its clearance into the CSF, leading to a measurable decrease in its concentration.

Alterations in CSF Aβ levels are detectable in the early stages of AD, and studies suggest that abnormal Aβ concentrations may appear years before the first subjective memory complaints, making Aβ42 one of the most crucial biomarkers for early disease detection. [21] This makes it the earliest known biomarker for Alzheimer's disease currently available in clinical diagnostics. As such, it enables the identification of pathological changes in the brain long before the emergence of clinical symptoms, opening new opportunities for early intervention and potential slowing of disease progression. [22]

Tau protein levels in the CSF reflect pathological processes associated with tau accumulation in the cerebral cortex. [23] Although phosphorylated tau (p-tau) is considered a more specific biomarker for Alzheimer's disease than total tau (t-tau), both markers play significant roles in diagnosis. [20,24,25]

Both t-tau and p-tau follow a similar pattern in the course of Alzheimer's disease, with their CSF levels increasing as the disease progresses. Their elevated concentrations are strongly associated with the accumulation of neurofibrillary tangles, serving as indicators of ongoing neuronal damage. [17,21,26,27] While elevated CSF tau is not exclusive to Alzheimer's, its levels correlate with the clinical progression of the disease, rising in parallel with worsening cognitive deficits. [26]

In the early stages of AD, decreased CSF Aβ42 is observed and is recognized as a predictor of progression from mild cognitive impairment (MCI) to AD. [27] Similarly,

increased levels of p-tau and t-tau in CSF can accurately predict the development of Alzheimer's disease in patients diagnosed with MCI. [28]

These biomarker changes can even be observed in cognitively normal individuals—abnormal Aβ and tau levels in CSF can be detected years before MCI diagnosis. [29–37] Interestingly, cognitively healthy individuals who are carriers of the apolipoprotein E ε4 allele (APOE4)—a genetic risk factor for late-onset Alzheimer's—also exhibit reduced CSF Aβ42 levels. [36,37] In familial Alzheimer's disease, studies have shown that asymptomatic carriers of PSEN1 and APP gene mutations display changes in CSF Aβ and p-tau levels more than 10 years before clinical symptom onset. [37–39]

**Imaging Biomarkers in Alzheimer's Disease (AD)**

Pittsburgh Compound B (PiB) is a specific ligand for Aβ, and when used as a tracer in positron emission tomography (PiB-PET), it allows for non-invasive in vivo analysis of both the presence and spatial distribution of amyloid deposits in the brain. Studies have shown that pre-mortem imaging with PiB-PET provides a direct measure of amyloid plaque burden, making it a valuable tool in the diagnosis of Alzheimer's disease. [40–46] Moreover, PiB-PET results show strong correlation with post-mortem findings, confirming its reliability as an indicator of amyloid accumulation in the AD brain. [46,47]

Additionally, PiB accumulation in the brain is inversely correlated with Aβ levels in the CSF, meaning that higher brain amyloid load corresponds to lower Aβ concentrations in cerebrospinal fluid. [28,31,48] This relationship supports the complementary use of fluid and imaging biomarkers in early detection.

The conversion from PiB-negative to PiB-positive occurs in the early stages of Alzheimer's, suggesting that amyloid buildup begins years before clinical symptoms emerge. [49] Among cognitively normal individuals, carriers of the APOE ε4 allele are at greater risk of converting to PiB-positive status, often years before the clinical onset of AD, compared to non-carriers. Furthermore, asymptomatic carriers of PSEN1 and APP mutations show greater PiB accumulation in the cortex and striatum, indicating early amyloid pathology. [50–52]

However, it is important to note that some cognitively normal older adults without known genetic risk factors can still present with positive PiB-PET scans. For this reason, PiB-PET imaging is recommended primarily in patients with additional clinical signs of dementia, to reduce the risk of false positives and ensure diagnostic accuracy. [23,30]

Although PiB-PET is recognized as a significant supportive biomarker in AD diagnostics, its use should be limited to cases with other clinical indicators of dementia to enhance the specificity of diagnosis. [53]

More recently, tau-specific ligands have been developed for PET imaging, enabling the visualization of tau pathology in the brain—a major advancement in the field. [54–56] While one might assume that Tau-PET could replace Amyloid-PET, recent studies suggest that combining both techniques provides a more comprehensive and effective means of monitoring Alzheimer's disease progression. [57,58]

**FDG-PET in Alzheimer's Disease**

Positron emission tomography using 2-deoxy-2-[18F]fluoro-D-glucose (FDG-PET) enables the assessment of glucose metabolism in the brain, serving as an indicator of neuronal and glial function. In Alzheimer's disease (AD), a reduction in FDG-PET signal is observed, reflecting glucose hypometabolism and synaptic dysfunction. These metabolic changes display a distinct topographical pattern that is characteristic of AD. [59]

Moreover, decreased FDG-PET signal correlates with lower synaptophysin levels in post-mortem studies, indicating loss of synaptic activity and ongoing neurodegeneration. [60,61] In patients with AD, bilateral reductions in FDG uptake have been documented in the temporal and parietal lobes, with particularly pronounced hypometabolism in the posterior cingulate cortex—a hallmark metabolic signature of Alzheimer's disease. [62,63]

In addition, FDG uptake is inversely correlated with cognitive impairment—that is, the lower the level of glucose metabolism, the greater the severity of cognitive deficits across the clinical spectrum of AD. [64] FDG-PET has demonstrated diagnostic sensitivity and specificity exceeding 80%, making it a reliable tool for evaluating disease progression in Alzheimer's patients. [65,66]

Even cognitively normal individuals who are APOE4 carriers exhibit glucose hypometabolism, suggesting the presence of early metabolic changes linked to Alzheimer's risk. [67,68] This hypometabolism is more pronounced in homozygotes than in heterozygotes, suggesting a dose-dependent effect of the APOE4 allele on metabolic dysfunction. [69] These alterations can be detected as early as the third decade of life, highlighting the presence of very early metabolic changes in APOE4 carriers. [70]

Finally, the introduction of novel PET tracers now allows for the estimation of regional distribution and total burden of tau pathology in vivo. Consequently, tau-PE has emerged as a

more sensitive biomarker for detecting the earliest cognitive changes in Alzheimer's disease compared to both Aβ-PET and cortical thickness measurements. [71]

**Structural and Functional Magnetic Resonance Imaging (MRI)**

Brain atrophy, particularly in the medial temporal lobe structures, can be quantitatively assessed using structural magnetic resonance imaging (MRI), enabling early detection of neurodegenerative changes characteristic of Alzheimer's disease (AD). [62,72] Such atrophy can be identified even before the appearance of clinical symptoms. Numerous studies confirm that medial temporal lobe atrophy, as assessed by MRI, is a reliable diagnostic biomarker for AD, supporting early identification of the neurodegenerative process. [73] Moreover, MRI serves as a neurodegeneration biomarker, enabling monitoring of disease progression and structural brain changes at various stages of Alzheimer's disease. [63,74]

This role is explicitly recognized in both the Dubois criteria [12] and the NIA-AA guidelines [20], where structural MRI is a core tool for evaluating neurodegeneration and disease progression. Its diagnostic sensitivity and specificity exceed 85%, making it a highly effective method for detecting structural brain changes in Alzheimer's disease. [62]

In the early stages of AD, the first detectable MRI changes include atrophy of medial temporal lobe structures, especially the hippocampus, as well as reduced cortical thickness in areas most vulnerable to Alzheimer's-related neurodegeneration. [75–83] Among asymptomatic carriers of APP mutations, hippocampal volume reduction has been observed 2–3 years before the onset of dementia, indicating early neurodegenerative changes preceding clinical symptoms. [84] In older adults, hippocampal volume loss may be detectable up to six years before dementia onset, underscoring the importance of early neurodegenerative diagnostics in AD. [74–79]

Additionally, abnormalities in the CA1 subfield of the hippocampus have been identified as early predictors of dementia in cognitively normal older adults, highlighting their pivotal role in Alzheimer's-related neurodegeneration. [76]

Furthermore, entorhinal cortex volume loss has been shown to precede cognitive decline by approximately four years, with a predictive accuracy of up to 90%, making it one of the most reliable early indicators of Alzheimer's disease progression. [77]

## When Does Alzheimer's Disease Begin?

The emergence of biomarkers has fundamentally shifted our understanding of Alzheimer's disease (AD). We have moved from a "static and defensive" model of pathogenesis to a more "dynamic and compensatory" perspective. Traditionally, brain changes leading to neuronal and synaptic loss—and ultimately cognitive decline—were thought to depend primarily on external damaging factors and the individual's structural brain reserve.

Contemporary models, however, acknowledge the individual variability in how people respond to early brain damage, the diverse intensity of pathological processes, and the effectiveness and adaptability of cerebral compensatory mechanisms. [85–87]

It is now well established that the key pathological processes in AD begin long before clinical symptoms, such as mild cognitive impairment (MCI), can be diagnosed. This notion is further supported by findings that these changes can begin decades before the first symptoms appear, during a period when individuals still display normal cognitive functioning. [88]

This paradigm shift increasingly highlights the importance of early therapeutic intervention, aiming to counteract biological disruptions before cognitive deficits emerge. [89]

## Biomarker Abnormalities Appear Before Clinical Symptoms

In the "dynamic biomarker cascade model", each biomarker reaches its peak intensity at a distinct stage of Alzheimer's disease (AD) progression, and this process occurs in a chronological and orderly sequence. Crucially, the highest levels of these biomarkers can be detected even before the appearance of any clinical symptoms.

In fact, numerous studies have shown that 20–40% of cognitively healthy older adults exhibit Aβ deposits in brain tissue. [90–92] Moreover, post-mortem examinations of elderly individuals without signs of dementia have confirmed the presence of Aβ plaques, further suggesting that amyloid deposition alone is not sufficient to cause cognitive decline. [93,94]
It has also been observed that neurofibrillary tangles—another hallmark of AD—may appear in individuals with no cognitive impairment. However, in asymptomatic individuals, these tangles are typically restricted to the entorhinal cortex (Braak stages I–II), whereas in symptomatic individuals, they are more widespread throughout the brain. [93,94]

PiB-PET imaging studies indicate that Aβ deposition may begin as early as two decades before clinical symptoms of dementia emerge. This is consistent with findings that CSF Aβ levels plateau by the time AD is diagnosed and no longer change significantly. Similarly, PiB

retention patterns remain stable across the course of the disease, further confirming early amyloid saturation. [88]

Previous research on AD has demonstrated that changes in Aβ and phosphorylated tau (p-tau) levels may occur more than 10 years before the clinical onset of the disease. [95] Most recently, researchers have documented sequential biomarker changes in cognitively normal older adults, tracking a progression from Aβ accumulation, through tau pathology, to cognitive impairment—thanks to repeated tau-PET and amyloid-PET measurements. [96]

All these findings support the central concept of the dynamic biomarker model: the existence of a latent (preclinical) phase of variable duration between amyloid plaque formation and the onset of neurodegeneration. This variability may stem from individual differences in Aβ processing, resistance to its neurotoxicity, and the efficacy of the brain's compensatory mechanisms. [97]

There is a growing body of evidence suggesting that Alzheimer's disease (AD) pathology may trigger compensatory brain mechanisms at various stages of the disease, with such mechanisms potentially being activated as early as the preclinical phase. However, there is still no clear consensus on the precise role these mechanisms play in cognitively normal individuals with positive AD biomarkers, or how they influence disease progression and the risk of conversion to dementia.

Lazarczyk and colleagues [95] sought to explore this issue in greater depth. They propose that compensatory mechanisms can be divided into two categories:

- Passive mechanisms, which align with the concept of cognitive reserve. These may delay the onset of dementia by allowing individuals to function normally despite underlying brain pathology.
- Active mechanisms, which might go beyond compensation by actively counteracting disease progression at a biological level—potentially halting the disease in the preclinical phase and thereby preventing conversion to dementia altogether.

This distinction highlights a promising area of research with significant implications for future therapeutic strategies aimed at enhancing the brain's resilience in the earliest stages of Alzheimer's disease.

**Anatomical Evidence of Compensatory Mechanisms**

Compensatory mechanisms in Alzheimer's disease (AD) can be observed anatomically through structural changes in the brain, particularly in asymptomatic carriers of presenilin 1 (PSEN1) mutations, when compared with age-matched control groups. [98] These individuals

show cortical thickening, primarily in temporal and parietal regions, with extensions into the precentral and postcentral cortices, as well as the pars triangularis.

Additional changes have been noted in posterior midline brain structures, including the anterior and posterior cingulate gyri. Importantly, no cortical thinning—a hallmark of symptomatic AD—is observed in these asymptomatic mutation carriers.

Interestingly, such structural compensatory changes are not exclusive to familial forms of AD. Studies have shown that cognitively healthy individuals with early signs of amyloid-β (Aβ) accumulation in sporadic Alzheimer's disease also exhibit similar patterns of increased cortical volume and thickness in regions typically vulnerable to AD pathology. [99]

However, as the disease advances, these initially hypertrophic regions begin to thin progressively, affecting both gray and white matter. In the symptomatic phase, this process culminates in extensive brain atrophy, which is characteristic of advanced-stage Alzheimer's disease. [100]

This transition—from early structural compensation to progressive degeneration—supports the view that the brain may initially attempt to resist or delay the pathological processes of Alzheimer's disease, but over time, these mechanisms are ultimately overwhelmed by the underlying neurodegenerative cascade.

**New Biomarker-Based Classification of Alzheimer's Disease**

Biomarkers are an increasingly valuable tool in both clinical practice and scientific research, especially in the context of human clinical trials, where they significantly enhance diagnostic accuracy. Their integration into research methodologies has led to a growing number of studies evaluating potential drugs to treat, alleviate, or manage Alzheimer's disease (AD)—although these efforts continue to face considerable challenges.

Given the substantial disconnect between the onset of pathological changes and the emergence of cognitive symptoms, a key concern arose: the risk of developing hypotheses that are unrelated to the actual pathophysiological mechanisms of AD. In response to this issue, the National Institute on Aging and the Alzheimer's Association (NIA-AA) proposed a new research framework for the use of biomarkers in both observational and interventional studies. [101]

This led to the creation of the A/T/N classification system, which categorizes individuals based on the presence or absence of specific biomarker types, using a binary approach (positive or negative):

- “A” (Amyloid): Biomarkers of β-amyloid deposition (amyloid PET or CSF Aβ42)
- “T” (Tau): Biomarkers of tau pathology (CSF phosphorylated tau or tau PET)
- “N” (Neurodegeneration): Biomarkers of neurodegeneration or neuronal injury (FDG-PET, structural MRI, or CSF total tau) [102]

An individual who is positive for A biomarkers is considered to fall within the “Alzheimer’s continuum”, meaning that AD-related pathological changes are present—even in the absence of clinical symptoms. Conversely, individuals who are positive for both A and T biomarkers are classified as having Alzheimer’s disease, as this combination reflects the coexistence of amyloid and tau pathologies, which together define the disease more specifically. [101]

The A/T/N system represents a shift toward a biology-based classification of AD, independent of clinical symptoms, allowing for a more objective and standardized approach to research, early detection, and ultimately, treatment development.

A recent study comparing the prevalence of biologically defined Alzheimer’s disease (AD) to that of clinically defined probable AD found that the biological form is more widespread, particularly among individuals aged 85 and older. This discrepancy is largely attributed to the presence of asymptomatic individuals who, based on the A/T/N classification, can be diagnosed with biological AD despite showing no clinical symptoms. [103]

As a result, this research framework defines Alzheimer’s disease based on its underlying pathology, detectable through biomarkers, rather than on clinical presentation alone. Although the A/T/N system is currently limited to research settings and not yet part of routine clinical practice, this new conceptualization of AD holds significant promise. It can enhance participant selection in clinical trials and support the development of novel therapeutic approaches aimed at intervening earlier in the disease course. [101,104]

Ultimately, the A/T/N framework represents a paradigm shift, redefining AD not as a condition diagnosed by symptoms alone, but as a biologically grounded disorder, potentially enabling earlier and more targeted intervention strategies in the future.

## Conclusions

Biomarkers play a crucial role in the early detection and monitoring of Alzheimer’s disease (AD). Their use enables the identification of pathological changes well before the onset of clinical symptoms, opening the door to early therapeutic intervention. The integration of biomarkers into the diagnostic process has significantly improved both the sensitivity and

specificity of AD diagnostics. While traditional criteria, such as NINCDS-ADRDA and DSM-IV, relied primarily on clinical symptoms, the modern approach incorporates advanced imaging techniques and cerebrospinal fluid (CSF) biomarkers.

Research shows that key pathological processes—such as the accumulation of beta-amyloid and hyperphosphorylated tau—begin decades before clinical symptoms emerge. It has been established that biomarker abnormalities can be detected more than 10 years prior to diagnosis. Increasing attention is also being given to compensatory mechanisms that may arise in response to early neurodegenerative changes. Structural brain changes, such as cortical thickening in specific regions, have been observed in asymptomatic carriers of AD-related mutations and in cognitively healthy individuals with amyloid-β accumulation.

The modern classification of AD, based on the A/T/N system proposed by NIA-AA, allows for more precise staging of the disease and facilitates more effective recruitment for clinical trials. Unlike previous models, this system defines Alzheimer's disease based on biological changes, not just clinical symptoms. The use of biomarkers in clinical trials supports better participant selection and more accurate evaluation of treatment efficacy.

Despite significant advances in diagnosis and disease monitoring, the development of effective drugs capable of halting or reversing neurodegeneration remains a major challenge. Ongoing research into biomarkers, compensatory mechanisms, and risk factors influencing disease progression is essential. Early therapeutic intervention continues to be a key objective in the fight against Alzheimer's disease, and the advancement of new diagnostic technologies may significantly improve treatment outcomes and patients' quality of life

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