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Review Article

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Revolutionizing Alzheimer's Diagnosis and Management: The Dawn of Biomarker-Based Precision Medicine

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ABSTRACT

Alzheimer's disease (AD), a leading cause of dementia, presents a formidable global health challenge intensified by the aging population. This review encapsulates the evolving landscape of AD diagnosis and treatment with a special focus on the innovative role of fluid biomarkers. Pathologically, AD is marked by amyloid beta (Aβ) plaques and neurofibrillary tangles of hyperphosphorylated tau, which lead to synaptic dysfunction, neuronal loss, and cognitive decline. These pathological changes, commencing decades before symptom onset, underscore the need for early detection and intervention. Diagnosis traditionally relies on clinical assessment, neuropsychological testing, and neuroimaging techniques. However, fluid biomarkers in cerebrospinal fluid and blood, such as various forms of Aβ, total tau, phosphorylated tau, and neurofilament light chain, are emerging as less invasive, cost-effective diagnostic tools. These biomarkers are pivotal for early diagnosis, differential diagnosis, disease progression monitoring, and treatment response evaluation. The treatment landscape is shifting toward personalized medicine, highlighted by advancements in Aβ immunotherapies, such as lecanemab and donanemab. Demonstrating efficacy in phase III clinical trials, these therapies hold promise as tailored treatment strategies based on individual biomarker profiles. The integration of fluid biomarkers into clinical practice represents a significant advance in AD management, providing the potential for early and precise diagnosis, coupled with personalized therapeutic approaches. This heralds a new era in combating this debilitating disease.

Keywords: Alzheimer's Disease; Amyloid Beta; Fluid Biomarker; Neurofilament Light Chain; Phosphorylated Tau

INTRODUCTION

Alzheimer's disease (AD) is a formidable challenge in global health, and is primarily driven by the rapid aging of the world's population. It is the most common cause of dementia, accounting for an estimated 60%–80% of all dementia cases,[1] and its impact is both profound and escalating. The total number of people suffering from dementia, which was at approximately 57.4 million as of 2019, is projected to skyrocket to an astounding 152.8 million by 2050.[2] This exponential increase underscores both a looming public health crisis, and a

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Conflict of Interest

The authors have no potential conflicts of interest.

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significant socioeconomic burden, with the global cost of dementia soaring from USD $(818 billion to an anticipated 2 trillion) from 2015 to 2030.[3] These figures paint a stark picture of a disease that is rapidly growing in prevalence and cost, posing a dire need for effective management and intervention strategies.

South Korea mirrors this global trend, with the country grappling with its own burgeoning AD crisis, particularly among its older population. Recent data have revealed that three-quarters of dementia cases in individuals over 65 years old are attributed to AD.[4,5] The number of older dementia patients, which stood at 794,280 in 2019, is expected to surge to 3,023,404 by 2050.[4,5] With the nation on the brink of entering a super-aged society in 2025,[5] the anticipated rise in dementia cases to over 1 million positions AD as a predominant health concern. This alarming trend has prompted the Korean Government and the Ministry of Health and Welfare to prioritize the prevention and treatment of AD, acknowledging its growing impact on the healthcare system and the nation's overall well-being.

From a pathological standpoint, AD is intricately complex.[6,7] It is characterized by the extracellular accumulation of amyloid beta (Aβ)-containing plaques and the ensuing Aβ-induced neuroinflammation (**Figs. 1A, C, 2A, and B**).[8] Compounding this is the development of intracellular neurofibrillary tangles, which are primarily composed of hyperphosphorylated tau protein (**Fig. 1A**). These pathological hallmarks of AD lead to progressive synaptic dysfunction and eventual neuronal loss (**Figs. 1B** and **2D**), culminating in cognitive decline and memory impairment synonymous with the disease (**Fig. 2E**). Understanding these pathological mechanisms is crucial for developing effective diagnostic and therapeutic interventions.

As the prevalence of AD continues to rise globally, the impact of the disease extends beyond the individual, straining healthcare systems and economies. Therefore, it is necessary to

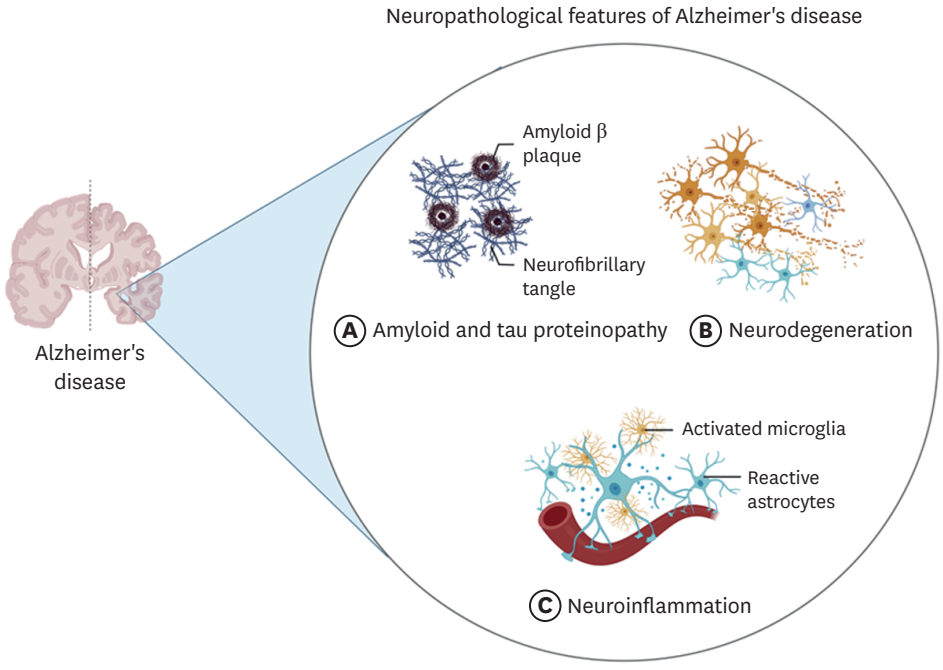

Fig. 1. Neuropathological features of Alzheimer's disease.

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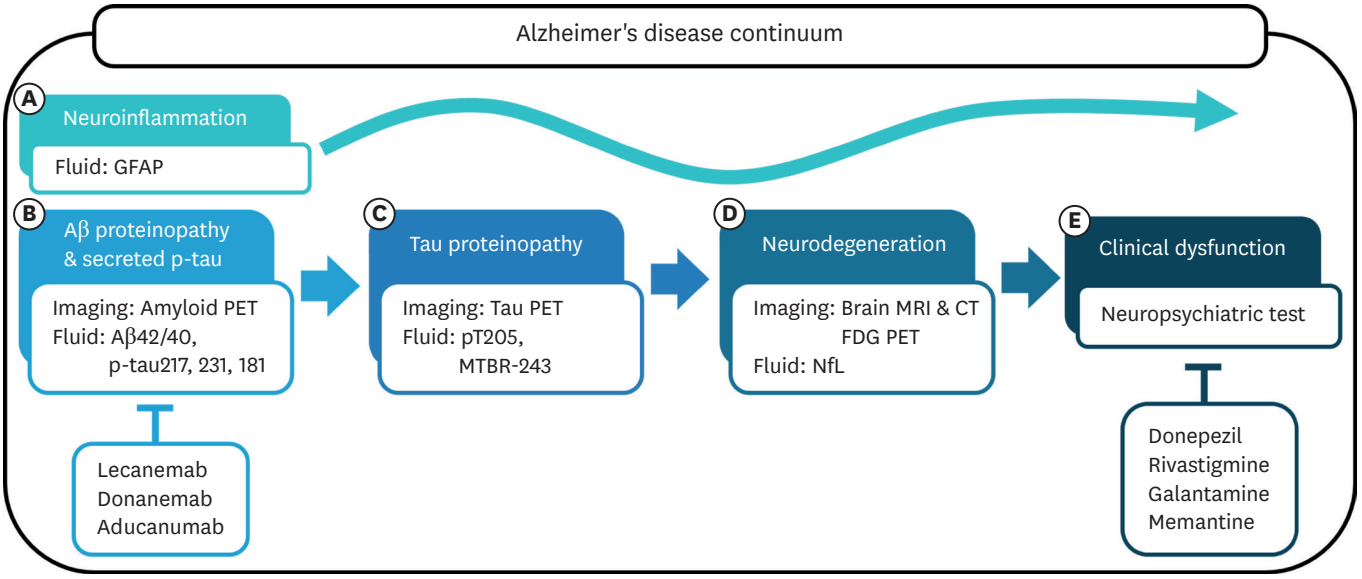

Fig. 2. Schematics of the AD continuum. (A) Amyloid proteinopathy is the initial neuropathological change of AD, which can be detected by amyloid PET or fluid biomarkers including Aβ42/40 and p-tau. (B) Anti-amyloid drugs, aducanumab, lecanemab, and donanemab, target amyloid. (C) The next stage is tau proteinopathy, which can be detected by tau PET or fluid biomarkers, including pT205 and MTBR-243. (D) Neurodegeneration can be monitored by anatomical brain MRI, FDG PET, or fluid biomarker NfL. (E) Finally, clinical symptoms appear. Medications including donepezil, rivastigmine, galantamine, and memantine, are targeting patients in this stage. Neuroinflammation, which can be monitored by GFAP, affects the progression of AD in diverse stages.
GFAP: glial fibrillary acidic protein, p-tau: phosphorylated-tau, PET: positron emission tomography, MTBR: microtubule-binding region, MRI: magnetic resonance imaging, CT: computed tomography, FDG: fluorodeoxyglucose, NfL: neurofilament light chain, AD: Alzheimer's disease.

urgently adopt advanced diagnostic techniques, effective treatments, and comprehensive management strategies.

This review shows the current state of AD by examining its epidemiology, pathology, and the strides being made in its diagnosis and treatment, particularly in the context of fluid biomarkers. By exploring these facets, we hope to shed light on potential pathways to mitigate the burgeoning impact of AD in an increasingly aging world.

PATHOLOGICAL PROGRESSION OF AD

AD initiates diverse pathological change in the human brain prior to the manifestation of clinical symptoms (**Fig. 2**). The earliest pathological change associated with AD is the deposition of Aβ peptides (**Fig. 2B**), which can start as early as two decades prior to the onset of mild cognitive impairment (MCI).[9,10] This early accumulation of Aβ is critical, as it sets the stage for the subsequent cascade of neuropathological events.[9]

As the disease progresses, tau proteins, another key biomarker of AD, undergo abnormal changes, resulting in hyperphosphorylation.[9,10] This leads to the formation of neurofibrillary tangles inside neurons, disrupting their normal function, and causing neuronal injury.[10] The interplay between the accumulating Aβ plaques in the brain and the formation of tau tangles is a hallmark of AD's progression. In particular, these tauopathies are closely associated with the cognitive decline characteristic of AD, indicating a direct correlation between the extent of tau pathology and the severity of cognitive impairment.[11]

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SYMPTOMATIC PROGRESSION OF AD

Symptomatically, AD does not adhere to a linear trajectory, but rather follows a continuum, spanning from preclinical stages marked by silent pathological changes, to eventual full-blown dementia.[12] In the preclinical phase, these pathological changes are often regionally limited, and can remain undetected for many years. However, with disease progression, subtle cognitive changes, including memory decline, gradually emerge, leading to MCI (**Fig. 2E**). At this stage, noticeable cognitive deficits manifest, though typically of a mild nature that do not significantly impair daily functioning. Eventually, these symptoms advance to dementia, where cognitive and functional abilities are severely compromised, thereby affecting the patient's ability to perform everyday activities.

AD DIAGNOSIS PATHWAY

In South Korea, the approach to diagnosing AD begins when individuals experience memory issues, consult primary care physicians, or visit public dementia centers. Healthcare providers play a crucial role in the early detection of potential cognitive problems; if objective cognitive impairment is identified, patients are typically referred to an AD specialist for further evaluation. The specialist's assessment is comprehensive, and includes a detailed medical history and neurological examinations to assess cognitive function and identify potential neurological deficits. These are followed by neuropsychological tests designed to evaluate various cognitive domains, such as memory, executive function, language, and visuospatial skills. To rule out other potential causes of dementia, laboratory tests are conducted, helping to exclude other conditions that might mimic or contribute to cognitive decline, such as vitamin deficiencies, thyroid disorders, or metabolic imbalances. Neuroimaging, including magnetic resonance imaging (MRI) and computed tomography scans, is employed to evaluate structural changes in the brain, rule out other neurological diseases, and provide supporting evidence for an AD diagnosis. Finally, for a more definitive diagnosis, cerebrospinal fluid (CSF) study or amyloid positron emission tomography (PET) scan may be performed, particularly in patients who meet specific criteria, such as younger patients presenting with progressive cognitive decline and suspected AD pathology, or to determine eligibility for anti-amyloid treatments. This scan allows the extent of amyloid plaque deposition in the brain to be visualized, and provides crucial information for the diagnosis of AD.

TREATMENT OPTIONS IN AD

In terms of treatment, contemporary pharmacological interventions for AD include drugs such as cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and the N-methyl-D-aspartate receptor antagonist memantine (**Fig. 2E**).[13] These medications aim to manage symptoms and improve quality of life, rather than cure the disease.[13] The choice of medication depends on various factors, including the stage of the disease, the patient's overall health status, and the presence of other coexisting medical conditions. The effectiveness of these treatments varies from person to person, and they are often used in combination with non-pharmacological approaches, such as cognitive therapy, lifestyle modifications, and support for caregivers.

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REVOLUTIONIZING AD MANAGEMENT: THE EMERGENCE OF PERSONALIZED MEDICINE AND ADVANCED THERAPEUTIC MODALITIES

Recent advances in the treatment of AD have ushered in a promising era, potentially transforming the therapeutic landscape with personalized treatment modalities. This evolution in care, often categorized as personalized medicine, is particularly critical in addressing the diverse manifestations and progression rates of AD in patients. Personalized medicine for AD involves tailoring treatment plans to individual patient profiles by considering genetic, biomolecular, and clinical factors. This approach is a departure from the traditional one-size-fits-all strategy, and is poised to revolutionize AD management.

A particularly exciting development in AD treatment is the advent of Aβ immunotherapies. These therapies are designed to target and clear Aβ, a protein that forms plaques in the brains of AD patients, and is believed to play a critical role in the pathogenesis of AD. Two such therapies, lecanemab and donanemab, have shown promising results in phase III clinical trials.[14,15] These monoclonal antibodies target distinct regions of Aβ 42, a specific form of the protein, and have been associated with significant reductions in amyloid burden in the brain.

In a clinical trial involving 1,795 patients over 18 months, lecanemab slowed the progression of AD symptoms by 27%, while also reducing the amyloid burden by up to 55%, although some adverse effects were reported, including infusion-related reactions, amyloid-related imaging abnormalities (ARIA)-H, ARIA-E, headache, and so on.[14] These results marked a relevant milestone in AD therapy. Furthermore, the trial indicated a notable decrease in phosphorylated tau (p-tau181) levels in the CSF and plasma, suggesting the potential of these biomarkers for monitoring treatment efficacy.

Similarly, in a clinical trial involving 1,736 patients, donanemab showed remarkable results.[15] Published in the *Journal of the American Medical Association* (*JAMA*), this trial reported an approximately 80% reduction in amyloid burden in the brain, along with a substantial reduction in plasma p-tau217 levels. Importantly, donanemab was effective in delaying the progression of AD symptoms across a combined population of patients. Some adverse effects were also reported including AREA-E, ARIA-H, headache, infusion-related reactions, and so on.[15]

Breakthroughs in Aβ immunotherapy are merely beginning, and the field of AD treatment is also exploring other innovative approaches, such as gene therapy and the use of nanoparticles. Gene therapy is still in its nascent stages for AD, with no ongoing phase 3 clinical trials yet.[16] But it allows genetic factors contributing to the disease to be directly addressed.[17] For example, several genes, including amyloid beta precursor protein, presenilin (PSEN) 1, PSEN2, apolipoprotein E(APOE)4, and glycogen synthase kinase-3β, are well-known targets for gene therapy.[18] Due to their size and versatility, nanoparticles hold promise in delivering drugs more effectively to the brain, allowing some of the challenges faced in treating neurological disorders to be potentially overcome,[19] with various drug-loaded nanocarriers under preclinical stages.[20]

In summary, the landscape of AD treatment is undergoing a considerable transformation. Personalized medicine, with its focus on individual patient profiles and the incorporation of novel treatment modalities, such as Aβ immunotherapies, gene therapy, and nanoparticles,

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is paving the way for more effective and targeted approaches to AD management. These advances offer hope for better clinical outcomes, while also underscoring the importance of early detection and intervention in altering the course of this debilitating disease. As research continues to evolve, the future of AD treatment appears to be increasingly promising, with the potential to significantly improve the quality of life of millions of patients worldwide.

NAVIGATING THE COMPLEXITIES OF AD TREATMENT: THE EVOLVING ROLE OF MONOCLONAL ANTIBODIES AND BIOMARKER-BASED THERAPIES

The development of drugs for AD-particularly in the realm of monoclonal antibodies targeting Aβ-has been both complex and enlightening. A cursory glance at the current landscape might give the impression that substantial strides have been made, with a few monoclonal antibodies showing positive results in clinical trials. However, this perception only skims the surface of a much more intricate and challenging process.

Delving deeper, it becomes evident that the pathway to effective AD drug development is fraught with obstacles. Although numerous compounds have been tested over the years with the aim of alleviating or reversing the symptoms of Alzheimer's, the vast majority have failed in clinical trials. This high failure rate highlights the immense challenges inherent in the development of successful AD treatments. The challenge is to not only find a compound that targets the pathology of the disease, but also to understand the intricate mechanisms of the disease, patient variability, and symptom progression.

A key issue in AD drug development is the selection criteria for clinical trial participants. Traditionally, patients with probable or possible MCI due to Alzheimer's, as per past clinical diagnostic criteria, were enrolled in these trials. However, a startling observation emerged from this approach: less than 20% of these patients progress from MCI to dementia within a two-year timeframe.[21] This slow progression rate presents a critical challenge to demonstrating the efficacy of a potential drug. To be deemed effective, a drug must show dramatic results in a relatively short trial period, which, given the slow progression of the disease in many patients, is difficult to achieve.

This challenge has led to a reevaluation of the strategies used in clinical trials. One promising approach is to enroll patients based on biomarkers, rather than clinical symptoms alone. Biomarkers provide a precise and objective measure of the disease's presence and progression, and offer an insight into its underlying pathology, which can be crucial to identify the appropriate patient population for clinical trials. This approach has been employed in recent trials for drugs such as lecanemab and donanemab, which have shown encouraging results.[14,15]

Lecanemab and donanemab represent a new wave of hope for AD treatment.[14,15] These drugs are designed to target Aβ in the brain, which is a key feature of Alzheimer's pathology. Trials for these drugs have been more successful than many previous efforts, partly because they have targeted patients whose disease progression can be tracked more accurately through biomarkers. This precision allows a clearer understanding of the impact of the drug on the disease, leading to more definitive conclusions regarding its efficacy.

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However, that is not the end of the matter. The complexity of Alzheimer's implies that no single drug is likely to be a cure-all. The disease manifests differently in different patients, progresses at varying rates, and has several contributing factors. Therefore, the future of AD treatment is likely to be a combinatorial approach, utilizing a range of therapies that are tailored to individual patient needs and disease characteristics.

In summary, while the development of monoclonal antibodies targeting Aβ in AD has seen some promising developments, the path toward effective treatment is far from straightforward. This involves overcoming substantial challenges in drug development, particularly in terms of patient selection for clinical trials. The shift toward the use of biomarkers for enrolment in these trials represents a relevant step forward, offering a more nuanced understanding of the disease, and a clearer pathway to assess drug efficacy. As research continues to evolve, it is hoped that these advances will lead to more effective and targeted treatments for AD, ultimately improving the quality of life of millions of patients worldwide.

TRANSFORMING AD DIAGNOSIS: THE EMERGENCE AND IMPACT OF BIOMARKERS IN CLINICAL APPLICATION

Current diagnostic criteria for AD predominantly rely on clinical data; however, consensus in the medical community regarding the necessity of a biological definition of AD is growing. This shift toward biologically-based characterization involves the utilization of biomarkers that reflect the underlying neuropathology of the disease. Biomarkers, which can be measured to indicate the presence of a disease, play a crucial role in various aspects of AD management. They can be instrumental in diagnosing the disease early, identifying its stage, assessing a prognosis, and gauging response to treatment. Furthermore, biomarkers are pivotal to understanding disease mechanisms and developing new treatment strategies.

Among the different types of biomarkers, imaging biomarkers have emerged as the most advanced, and are widely used in clinical trials. Contemporary methods allow the careful selection of the most suitable candidates for clinical trials using brain MRI, PET, and Tau PET. The advance in imaging biomarkers has provided critical insights into the disease's pathology,[22] revealing that Aβ deposition, a hallmark of AD, occurs approximately 20 years before the onset of clinical symptoms.[23] This is followed by tauopathy, which manifests a few years later. These pathological changes have detrimental effects on brain structure, precipitating memory and cognitive decline.[23]

In 2018, a substantial development occurred with the release of the National Institute on Aging–Alzheimer's Association's (NIA-AA) research framework,[24] which recommended the adoption of criteria based on a biological definition of AD.[24] To conduct clinical trials for the treatment of AD, it advised to enroll patients with at least an amyloid pathology positive status. This recommendation marks a shift toward a more biomarker-focused approach to the diagnosis and understanding of AD.[24]

The revised criteria set forth by the NIA-AA were published in 2024, defining AD biologically to bridge the gap between research and clinical practice.[25] The updated diagnostic criteria incorporate fluid biomarkers in the CSF and blood, along with imaging biomarkers.[25] Biomarkers such as Aβ42 and amyloid PET are utilized for amyloid pathology (denoted as "A"). P-tau217, p-tau181, and p-tau231 are phosphorylated forms of tau associated with AD

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that become elevated around the same time as amyloid PET positivity. Biomarkers include PT205, MTBR-243, non-phosphorylated tau fragments, and Tau PET for tau pathology ("T"), neurofilament light chain (NfL) and MRI or CT, as well as fluorodeoxyglucose (FDG) PET for neurodegeneration ("N"), and glial fibrillary acidic protein (GFAP) for inflammation ("I"). The biomarkers are categorized into Core 1 for the early stage of AD, and Core 2 for the more advanced stage. This categorization implies that AD diagnosis and patient selection can be based on the results obtained from CSF and blood tests.

The potential for diagnosing AD based on fluid biomarkers in the near future is a topic of considerable interest and debate. Currently, CSF is already being employed for the diagnosis of AD, especially with recent developments, such as the approval of Roche's Elecsys-II in Korea and the US.[26] Advances in the field suggest a strong likelihood that blood-based diagnostics for AD will soon become a reality, given the consistent and reliable results observed globally.

Fluid biomarkers have diverse applications in the treatment of AD; they can be used for early diagnosis, differential diagnosis, monitoring of the disease course, and assessment of treatment effectiveness.[27] Various fluid biomarkers derived from different sources are detectable in both CSF and blood. Some of these biomarkers are detectable in both media, whereas others are exclusive to CSF. The list of available fluid biomarkers in the CSF is extensive.[28] Biomarkers detectable in blood include Aβ40, Aβ42, the Aβ42/40 ratio, total tau, phosphorylated tau (p-tau) at different sites (p-tau231, p-tau217, p-tau181), NfL, and GFAP, highlighting the potential for less invasive diagnostic procedures.[29, 30]

When considering the efficacy of different biomarkers, it is important to weigh various factors, such as cost, invasiveness, and ease of repetition. Considering these factors, blood-based biomarkers are emerging as the most favorable; nevertheless, it is crucial to acknowledge that imaging biomarkers exhibit the highest accuracy.

Recent studies on blood biomarkers for AD, including the p-taus, NfL, Aβ42/40 ratio, and GFAP, have shown promising findings that support the possibility in the near future of AD diagnosis using blood tests. Such a development would mark a substantial advancement in the field, offering a less invasive, more accessible, and potentially more cost-effective method for the diagnosis and management of AD.

ADVANCES IN FLUID BIOMARKERS FOR AD: A COMPREHENSIVE ANALYSIS OF DIAGNOSTIC POTENTIALS AND CHALLENGES

Hereafter, we aim to elucidate the significance and potential of fluid biomarkers in the diagnosis of AD by drawing on real data and collaborative research. In our previous study,[31] our focus was on the measurement of Aβ42 in the CSF using the Enzyme-linked Immunosorbent Assay technique. Our findings align with the hypothesis that CSF Aβ42 levels are significantly lower in individuals with amyloid–positive pathology, compared to those in the amyloid–negative group.[31] This discrepancy underscores the potential of Aβ42 as a diagnostic marker in distinguishing AD from non-AD conditions.

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While extending our research to measure plasma Aβ in the same cohort, we encountered limitations in accuracy that rendered the results insufficient to effectively differentiate AD patients from non-AD participants. However, the recent literature has suggested that when measured using specialized techniques, plasma Aβ might offer diagnostic value.[32] A review of current methodologies revealed a considerable variance in the diagnostic efficacy of plasma Aβ, contingent upon the measurement technique employed. Ionization-Mass Spectrometry exhibited superior performance, while single molecule array (SIMOA) technology did not yield comparable results.[32]

The narrative changes significantly when we consider p-tau proteins. P-tau exists in various forms, including p-tau181, p-tau199, p-tau231, and p-tau217. Emerging research has proposed the potential of plasma p-tau181 in diagnosing early-stage AD, as demonstrated in two distinct studies,[33,34] These data indicate a specific increase in plasma p-tau181 levels in AD, unlike in other conditions. Furthermore, plasma p–tau181 levels begin to rise at least eight years before the onset of clinical symptoms.[35] These findings suggest that plasma p-tau181 could be a valuable biomarker for the diagnosis of MCI and early dementia attributable to AD. In recent clinical trials, such as those for lecanemab, plasma p-tau181 levels have been monitored to assess the progression and treatment response in patients with AD.[14]

Another study that compared various plasma biomarkers revealed that a combination of p-tau231 and Aβ42/40 ratio measured via Mass Spectrometry might be slightly more effective than a combination of p-tau181 and Aβ42/40 ratio measured by SIMOA.[36]

Recent consensus in the field points to p-tau217 as a promising candidate among plasma biomarkers. Reports indicate its high diagnostic value and potential to predict the progression of AD from MCI to dementia, as shown in the presented slide.[37] Plasma p-tau217 had equivalent diagnostic performance to CSF p-tau217 for detecting amyloid-PET positivity, while p-tau213 and p-tau181 did not.[38] Plasma p-tau217 was also utilized in a clinical trial for donanemab to monitor patient progression.[15]

In a comparative study,[34] plasma p-tau231 levels first increased in the early stages of AD, whereas p-tau217 demonstrated the highest discriminative value, with p-tau181 occupying an intermediate position. The plasma p-tau217 outperformed p-tau181 and p-tau213 in predicting amyloid positivity.[25] Although we can now analyze p-tau217 with commercially available immunoassay,[39] the global applicability of p-tau217 was hampered until 2023 by the unavailability of commercial kits, which posed a substantial limitation. In contrast, p-tau181 does not face such patent issues, leading to the availability of various kits and numerous research. Many studies have validated the reproducibility and generalizability of p-tau181 in the diagnosis of AD.

We now focus on the intricate details of our studies demonstrating the potential role of blood biomarkers as predictors of amyloid PET positivity. This investigation focused on the measurement and analysis of several key blood biomarkers in two distinct cohorts: Asan and KBASE-V.[40,41]

The biomarkers in question include p-tau at 181 (p-tau181), apoE status, NfL levels, and Aβ42/40 ratio. The study's findings reveal that a combinatory analysis of these four blood biomarkers holds a significantly high predictive value, with a high area under the curve (AUC) across all participants.[40] Notably, the standalone measurement of p-tau181 itself displayed a substantial predictive value,[40] which indicates the potential utility of these biomarkers in

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clinical settings for the early detection of AD. Further stratification of participants based on their dementia status shows that this combination of biomarkers demonstrated better AUC values, particularly in participants with dementia. Such data underscore the efficacy of these biomarkers, not only in detecting amyloid pathology, but also in distinguishing between various stages of cognitive impairment.

The subsequent phase of the study aimed to assess the ability of blood biomarkers to predict cognitive-stage transitions. For this purpose, we measured plasma p-tau181, cortical thickness, hippocampal volume, amyloid positivity, cognitive function, and demographic factors in the KBASE-V cohort. Our results indicated that a combination of plasma p-tau-181, centiloid value from amyloid PET, age, and semantic fluency presented a high predictive ability for cognitive stage transitions within a 3-year timeframe, with considerably high probabilities.[41] When focusing on participants with MCI, the predictive accuracy, as denoted by the AUC, was remarkably higher. This finding suggests that with these biomarkers, it is possible to predict MCI progression with a high degree of certainty.

GFAP has recently emerged as a notable biomarker in Alzheimer's research. A study published in Nature Medicine this year highlighted the critical role of astrocytes in the progression of AD pathology, particularly in the preclinical stages.[42] The study posited that detecting abnormalities in astrocyte reactivity biomarkers in the blood is essential to predict the development of tau pathology and subsequent clinical symptoms in individuals who are cognitively unimpaired, yet Aβ positive.[42]

Initially, it was hypothesized that the NfL could be a specific biomarker for AD.[43] However, this notion has evolved; while NfL is no longer considered AD–specific, consensus has been reached on its value as a fluid biomarker to evaluate neurodegeneration.[44] Current methodologies do not permit the diagnosis of neurodegenerative diseases based solely on serum NfL levels; nevertheless, their potential to assess the extent of neurodegeneration, and possibly the therapeutic effects of treatments, is significant. Notably, in our previous study,[45] serum NfL level demonstrated a strong correlation with brain atrophy, particularly in regions such as the hippocampus and medial temporal lobe.

Soluble triggering receptor expressed on myeloid cells 2 (sTREM2) was a focal point of interest following genome-wide association studies that identified a TREM2 mutation as a significant genetic factor in AD.[46,47] In our research involving the Asan cohort, we measured plasma soluble TREM2. Our findings indicated that plasma sTREM2 was not specific to AD, but rather showed a high correlation with age.[31] We now understand that plasma sTREM2 originates from peripheral macrophages, reducing its specificity as a biomarker for AD.[48]

In another segment of our study, we compared several fluid biomarkers in the CSF and plasma, and found that while some biomarkers showed high correlations between the CSF and plasma, others did not.[31] This underscores the need for careful consideration when employing blood biomarkers for the diagnosis and follow-up of AD, as certain plasma biomarkers may not correlate well with their CSF counterparts.

In summary, various fluid biomarkers detectable in both CSF and plasma have been consistently linked to alterations in Aβ levels, beginning approximately 20 years before symptom onset. Subsequent changes in p-tau217 and p-tau181 follow a well-established sequence,[49] enabling the potential diagnosis of AD based on fluid tests.

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TRANSFORMING AD MANAGEMENT: THE INTEGRAL ROLE OF FLUID BIOMARKERS IN CLINICAL TRIALS AND DIAGNOSIS

Recognizing the burgeoning role of blood biomarkers in AD research, the Clinical Trials on Alzheimer's Disease (CTAD) task force conducted an exhaustive review of several clinical trials that incorporated these biomarkers.[50] Their comprehensive analysis, published June 13, 2023, provides critical insights into the evolving landscape of AD diagnosis and management. The taskforce's findings underscore the increasingly prevalent use of various blood biomarkers in the prescreening stages of recent phase 2 and 3 clinical trials.[50] This strategy has been instrumental in refining the selection process for participants, particularly focusing on individuals who exhibit heightened suspicion for AD based on initial biomarker assessments.

One notable example is the ongoing TRAILBLAZER-ALZ3 clinical trial (https://classic.clinicaltrials.gov/ct2/show/NCT05026866), which exclusively utilizes plasma p–tau217 as a screening tool.[50] The decision to rely on p-tau217 reflects a growing confidence in the specificity and sensitivity of this particular biomarker in identifying individuals at various stages of AD. This targeted prescreening approach helps streamline the clinical trial process, enabling a more efficient and accurate identification of suitable candidates for further investigation.

The advancing understanding and application of fluid biomarkers have also influenced ongoing revisions of the diagnostic criteria for AD, specifically within the context of the 2024 revised criteria and staging of AD.[25] The general consensus is that the integration of fluid biomarkers into diagnostic criteria represents a considerable step forward, and current suggestions that heavily incorporate the use of fluid biomarkers are unlikely to undergo substantial changes. This underscores the need for the medical community to familiarize itself with the nuances and applications of fluid biomarkers in AD diagnosis and management.

In clinical trials, fluid biomarkers for AD fulfill critical functions, including prescreening, screening, and patient monitoring.[51] Their utility extends beyond the research setting to clinical practice, where these biomarkers offer substantial advantages. For example, in the prescreening of patients with AD, fluid biomarkers are a cost-effective and less invasive alternative to amyloid PET imaging. This approach is particularly advantageous, given the high costs and limited accessibility associated with PET imaging.

Moreover, fluid biomarkers are invaluable in the context of prescribing new and often expensive pharmacological interventions, such as lecanemab and donanemab.[14,15] These drugs, which represent the cutting edge of AD therapy, require precise patient selection to ensure both efficacy and cost-effectiveness. Biomarkers aid in this selection process by providing objective and quantifiable data that can inform clinical decision-making.

Fluid biomarkers are instrumental in the early evaluation of therapeutic efficacy. Upon initiating new treatments, it is imperative to monitor their impact accurately and efficiently. Fluid biomarkers offer a means of tracking disease progression and treatment response in real-time, providing clinicians with vital information to adjust therapeutic strategies as needed.

In conclusion, the integration of fluid biomarkers into the diagnostic and therapeutic landscape of AD represents a pivotal advancement in the approach to this complex and

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challenging condition. As research continues, the potential of these biomarkers to transform the diagnosis, management, and treatment of AD becomes increasingly apparent. The medical community must therefore remain abreast of these developments, integrating fluid biomarkers into clinical practice to enhance patient care and treatment outcomes in AD.

CONCLUSION

It is pertinent to underscore that the field of AD diagnosis and treatment is undergoing a transformative shift, propelled by the advances in precision medicine. Historically, the diagnosis of AD has been predominantly based on clinical observations and symptomatology. However, with the emergence and refinement of imaging technologies such as MRI and PET, a substantial leap toward more accurate and precise diagnostic methodologies has been made.

The future trajectory of AD management is expected to be significantly influenced by the incorporation of various fluid biomarkers into clinical practice. These biomarkers can revolutionize the process of diagnosing and monitoring AD, facilitating the implementation of more personalized and targeted therapeutic interventions. Accurate and early diagnosis made possible by these advances allows the application of a spectrum of treatment modalities that are specifically tailored to the individual patient's stage and characteristics of the disease.

For example, in patients with MCI or early-stage dementia attributable to AD, interventions may include the modulation of modifiable risk factors and administration of Aβ immunotherapies. These strategies aim to intercept and mitigate disease progression at an early stage. In contrast, for patients with more advanced stages of dementia due to AD, therapeutic approaches may align more closely with the current standards of care, focusing on symptom management and enhancing the quality of life.

Regarding the horizon of AD treatment, emerging therapies, such as gene therapy and the use of nanoparticles, are potential groundbreaking modalities. These novel approaches are indicative of the ongoing evolution in the field, reflecting a shift toward more innovative and potentially more effective strategies to combat the complexities of AD.

The landscape of AD diagnosis and treatment is evolving rapidly, driven by technological and scientific advances. The integration of these new tools and methods promises to bring about a more nuanced understanding of the disease, and open new avenues for the effective management and treatment of AD.

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