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Advancing Alzheimer's Diagnosis: The Role of AI - A Review

Dominika Rehan - **corresponding author**
e-mail: dominikarehan3@gmail.com
ORCID: https://orcid.org/0009-0000-9796-599X
Lower Silesian Center for Oncology, Pulmonology and Hematology, Plac Ludwika Hirszfelda 12, 53-413 Wrocław, Poland

Sven Solisch
e-mail: solisch.sven@gmail.com
ORCID: https://orcid.org/0009-0002-4769-6095
University Clinical Hospital in Opole, Wincentego Witosa 26, 45-401 Opole, Poland

Anna Blazhkova
e-mail: blazhkova.anna@gmail.com
ORCID: https://orcid.org/0009-0008-4826-4810
T. Marciniak Lower Silesian Specialist Hospital – Emergency Medicine Centre.
ul. Gen. Augusta Emila Fieldorfa 2, 54-049, Wrocław, Poland

Anna Susłow
e-mail: asuslow@gmail.com
ORCID: https://orcid.org/0009-0004-2745-3971
T. Marciniak Lower Silesian Specialist Hospital – Emergency Medicine Centre.
ul. Gen. Augusta Emila Fieldorfa 2, 54-049, Wrocław, Poland

Adam Szwed
e-mail: ac.szwed@gmail.com
ORCID: https://orcid.org/0009-0008-8614-6292
Wroclaw Medical University, Jana Mikulicza-Radeckiego 4A, 50-372 Wrocław, Poland

Ewa Szczęsna
e-mail: szczesnae17@gmail.com
ORCID: https://orcid.org/0009-0001-4767-7356
Lower Silesian Center for Oncology, Pulmonology and Hematology, Plac Ludwika Hirszfelda 12, 53-413 Wrocław, Poland

1. ABSTRACT

Introduction: Alzheimer's disease (AD) is a progressive neurodegenerative disease that accounts for more than half of all cases of dementia worldwide. An aging society therefore poses a huge challenge to medicine. The exact mechanism responsible for this disease is still not fully understood. However, theories of neurodegeneration related to the deposition of pathological proteins in the brain and the imbalance between individual neurotransmitters have allowed the development of effective diagnostic methods - laboratory determination of specific biomarkers (tau protein, β-amyloid) and their marking using PET (Amyloid PET, Tau PET). Magnetic resonance imaging (MRI) is also important in diagnostics. Artificial intelligence (AI) is a promising, new, and rapidly developing path that can significantly affect the diagnostic process of Alzheimer's disease.

Purpose of the study: This review examines the role of AI in diagnosing Alzheimer's disease.

Materials and methods: A comprehensive literature review was conducted, analyzing 63 studies from the PubMed database (in English, up to December 2024) that assessed the effectiveness, methods, and prospects of AI in the diagnosis of Alzheimer's disease.

Conclusions: Share of AI in the diagnosis of Alzheimer's disease is extremely promising. AI used in neuroimaging, genetics, and behavioral biomarkers shows great potential diagnostic. AI-based tools are extremely promising because they can be non-invasive and highly sensitive biomarkers. Optical coherence tomography (OCT) and OCT angiography (OCTA) combined with AI models offer an opportunity for cost-effective and rapid diagnostic pathways for AD. This review presents evidence that artificial intelligence is a key factor in transforming AD diagnostics into modern diagnostics that enable earlier detection and treatment of the disease which may consequently positively impact the quality of life of AD patients and their caregivers.

Keywords: Alzheimer's disease, neurodegenerative disease, dementia, AI, artificial intelligence

1. INTRODUCTION

People in the modern world live longer - undoubtedly thanks to technological achievements enabling earlier detection of diseases and their more effective treatment and greater public awareness of their health. These two issues can be considered to be the success of public health [1, 2]. However, on the other hand, the image of an aging society is associated with an inevitable problem in the form of an increase in cases of Alzheimer's disease (AD) [3]. AD is a neurodegenerative disease that is more than half of all cases of dementia in the world [4]. Only in the United States, over 5 million people are suffering from AD, and by 2050 this number is to triple according to WHO calculations (in the Polish population it is estimated that in 2050 about 1 million people will be affected by AD) [5, 6]. It will be an important element of the future health policy in the world because AD is manifested by memory disorders, behavior, and problems related to proper functioning in everyday life. AD's risk factors include, among others: age, female sex, low education, Down syndrome, depression, and the occurrence of a family disease. However, the most important protective factor is higher education [7]. The exact AD mechanism is still not fully understood, but some interesting theories were created explaining the observed symptoms. These are

primarily - neurodegeneration associated with the deposition of pathological proteins in the brain of people suffering from AD and disorders in equilibrium between individual neurotransmitters [8].

The most important hypothesis remains the formation of plaques made of β-amyloid (Aβ). It is an abnormal protein that arises from the precursor protein of amyloid (APP) as a result of incorrect post-translational modifications - the action of incorrect enzymes, secretase [9]. As a result of the accumulation of Aβ, nerve cells are destroyed in the area of the formation of the elderly plaques and the growth of cognitive deficits [10]. It results from this extracellular nature of Aβ. In contrast, an intracellular protein associated with AD is called the tau protein [8]. Physiologically it stabilizes the cytoskeleton due to connections with microtubulas. Unfortunately, in the course of AD, the tau protein is hyperphosphorylated, which leads to neurofibrillar degeneration [11]. As a result of the processes described above, the regulation of intercellular communication is disturbed, including synaptic transmission. This, in turn, directly leads to the disproportion between individual neurotransmitters [8]. The most important in terms of AD seems to be the impairment of cholinergic transmission because this system plays a key role in cognitive processes [12]. Reduced acetylcholine (ACh) levels are associated with an increased level of acetylcholinesterase (AChE) expression - the enzyme responsible for metabolism - promote the creation of plaques built of Aβ and worsens the course of the disease [13]. Interestingly, in recent years, more and more often in the course of AD is paid attention to changes in the levels of other neurotransmitters, including noradrenaline and serotonin. It was noticed that lowering noradrenergic impulse in locus coeruleus is responsible for problems with memory or learning new things [14]. In addition, it was discovered that degeneration of serotoninergic neurons within the raphe nuclei of the brain stem is associated with memory loss [15]. Another AD development hypothesis applies to oxidative stress and related mitochondria dysfunction. The overproduction of reactive oxygen species (ROS) is associated with difficulties in removing Aβ plaques, and thus faster development of AD symptoms [16].

The latest and at the same time the most interesting seem to be theories taking into account the participation of the immune system or intestinal microbiota in the pathogenesis of AD. Both of these concepts are based on increased NO synthesis, respectively by overactive cells of the nervous system in response to stimulation by the cells of the immune system or microorganisms inhabiting our digestive tract [17, 18]. It has been proven that the increased NO level causes neurodegenerative changes and can lead to the development of many

pathologies within the nervous system [16]. All of the above processes lead to interneuronal communication disorders, which are the basis for clinical symptoms.

The multitude of the above theories, their complex nature, and the multitude of clinical implications encourage modern scientists to use artificial intelligence (AI) technology, to best learn not only pathomechanisms responsible for AD development but also for quick diagnosis and effective treatment in the future [19]. The legitimacy of applying AI in AD is noticed primarily in minimizing social exclusion and providing the longest life not requiring the help of other people, and not only in strictly medical issues [5].

2. STATE OF KNOWLEDGE

2.1. Alzheimer's disease diagnosis - methods

The recommendations for diagnosing Alzheimer's disease have evolved over the past decades. Diagnosing and staging AD may involve considering multiple factors, including clinical presentation, laboratory tests, and neuroimaging. However, what defines AD, rather than clinical syndromes observed in this condition, are the unique pathophysiological mechanisms that affect the brain and lead to the emergence of symptoms. Therefore the specific biomarkers, the β-amyloid and the tau protein, are essential for establishing a diagnosis of AD. These biomarkers can be detected through laboratory tests involving plasma and cerebrospinal fluid assays as well as in positron emission tomography (PET) which utilizes AD-specific techniques targeting the abnormal proteins in contrast to less specific methods like MRI [20].

MRI (Magnetic resonance imaging) is an important diagnostic tool in AD. It safely allows imaging of brain structures without the use of ionizing radiation. Advanced techniques like volumetric MRI enable the measurement of specific brain structures such as the hippocampus, which is frequently subject to atrophy in early-stage AD.

Apart from detecting structural changes associated with AD, such as brain atrophy, MRI is useful in ruling out other conditions like tumors or vascular dementia. MRI, however, does not detect amyloid or tau protein accumulation [21].

Amyloid PET is a diagnostic imaging technique used to detect β-amyloid plaques in the brain tissue. It involves the administration of a radiotracer, (e.g. ^{18}F-florbetapir, ^{18}F-florbetaben, or ^{18}F-flutemetamol), which binds to amyloid plaques. After the tracer is injected the patient undergoes a PET scan to reveal the presence and distribution of amyloid deposits.

This method is particularly indicated in cases of diagnostic uncertainty such as atypical or mixed dementia symptoms, persistent MCI (mild cognitive impairment), or dementia with early onset (before 65 years). A positive amyloid PET scan supports a diagnosis of AD when combined with clinical and cognitive evaluations, while a negative scan essentially rules out AD as the underlying cause of cognitive symptoms [22].

Amyloid PET has, however, some limitations. For instance, the test does not give information on either the severity of the disease or the rate of its progression and more importantly it cannot differentiate AD from some other amyloid-related disorders such as cerebral amyloid angiopathy [23].

In contrast, Tau PET is employed to identify aggregates of tau protein. It also employs radiotracers such as ^{18}F-flortaucipir and more recent ^{18}F-PI-2620 which bind to abnormal tau deposits. A PET scan helps in displaying the distribution of tau protein in the brain in detail through images. This technique is also useful in cases of diagnostic uncertainty in atypical or early-onset dementia cases [24]. Exclusions apply to possible off-target binding at places like neuromelanin and monoamine oxidases [25].

Both tau and amyloid PET imaging are characterized by high costs and require advanced equipment, and therefore their application is limited to specialized units. Despite these challenges, they remain important tools for improving diagnostic accuracy and guiding treatment decisions for AD [22, 24].

2.2. Artificial intelligence and current diagnostics

Artificial intelligence models that were applied to brain MRI scans have had remarkable success in diagnosing Alzheimer's disease in its early stages. Convolutional Neural Network (CNN) initially stood out as a leading architecture. It has a classification accuracy of more than 90% in segregating AD from healthy individuals and individuals with mild cognitive impairment [26, 27].

For instance, multi-class classification tasks that distinguish between diagnostic categories like Non-Demented, Very Mild Demented, Mild Demented, and Moderate Demented have achieved test accuracies as high as 96.87%, with near-perfect ROC AUC values across all classes [28]. Combined methods and transfer learning further improve model performance on a variety of datasets [29].

CNN-based models have been intensively compared with other models, including ResNet50 and VGG16, to check their relative performance of AD diagnosis. The results show that CNN outperforms the mentioned models in terms of sensitivity and specificity. They

managed to achieve a classification accuracy of 97% across several stages of AD, mainly due to its simplicity, and also computational efficiency [30]. That makes it considerably more useful for managing large MRI datasets.

- **Eye-tracking technology**

AI is a promising tool for analyzing eye movement patterns. Eye-tracking technology combined with deep learning algorithms offers us the non-invasive, cost-effective, and most importantly effective possibility to identify AD-related cognitive impairments. Research has shown that patients with AD present behavioral general eye movements which include impairment of saccadic function, and short immobilization time. Those patterns also include abnormal visual attention that reflects underlying neurological impairments and provides valuable biomarkers for early diagnosis of the disease, disease staging, and progression of disease monitoring.

In one broad study, researchers investigated the association of eye movements with AD risk using AI-based computer vision. The present study analyzed eye-tracking data from individuals at different cognitive stages by using deep learning models that could identify specific saccadic patterns linked to cognitive decline. This method accomplished more than 85% diagnostic accuracy when distinguishing AD patients from healthy individuals. The main markers were delays in saccadic reaction times, including increased latencies and reduced amplitudes [28]. These findings highlight the possibility for AI-powered eye-tracking systems to further improve conventional diagnostic tools by providing accessible quantitative assessment tools of cognitive function.

Another study investigated the use of eye-tracking data in integrated multi-modal AI models for diagnosis. Eye movement measurements of the fixation dispersion, saccadic reaction times, and gaze entropy significantly improved diagnostic algorithm performance when combined with neuroimaging and blood biomarkers. Indeed, this integrated approach yielded an AUC of 0.92 or a 7% increment over single-modality models [31]. Importantly, fixation patterns reflecting shifts in attention during cognitive tasks were especially predictive of the early stages of AD and highlighted the added value of eye-tracking data in a broader diagnostic pipeline.

In another investigation, the clinical scalability of AI-powered eye-tracking technology was tested by the development of portable, machine learning-equipped devices to allow for rapid dementia screening in real-world settings. These devices, which can analyze gaze metrics in only a few minutes, were able to effectively detect visual attention deficits

among MCI and early-stage AD participants. They managed to achieve a sensitivity of 89% and a specificity of 87%, which has made it useful for everyday clinical practice [32]. This technique can solve one of the major challenges facing the dementia diagnostic modality, which relies more on invasive and expensive CSF analysis or even the use of PET imaging, especially in resource-poor settings. The portability of these devices improves their potential for use in real-life settings.

Beyond diagnosis, AI-based eye-tracking technology gave us valuable insights into the progression of AD. Longitudinal studies using RNNs have shown that changes in gaze metrics over time, such as increased variability of fixation stability and longer gaze fixations on irrelevant stimuli, are strongly correlated with cognitive decline. In one such study, eye-tracking data from individuals over three years was tracked to predict the progression from MCI to AD with an accuracy of 82% [31].

These findings show that eye movement tracking can be a reliable tool for identifying patients at higher risk of rapid disease progression, thus making possible an early intervention and patient-tailored treatment.

- **PET Imaging and AI**

Recent improvements in deep learning, a subset of artificial intelligence (AI), have shown promise for analyzing fluorodeoxyglucose positron emission tomography (FDG PET) images for the diagnosis of Alzheimer's disease (AD) and mild cognitive impairment (MCI). A recent study identified metabolic abnormalities associated with AD using convolutional neural networks CNNs. Glucose hypometabolism in the hippocampus, posterior cingulate cortex, and temporoparietal regions mentioned previously are associated with the diagnosis of AD.

The AI models demonstrated significant diagnostic accuracy, achieving classification rates exceeding 90% for the separation of AD patients from healthy controls [33]. Sensitivity and specificity metrics were also high for detecting MCI, underscoring the models' potential to identify early cognitive decline during the transitional phase between healthy aging patients and AD patients. This, consequently, lowers clinical doctors' dependence on subjective interpretation while providing a method that can ensure consistency and is at the same time expandable.

- **Circulating Cell-Free DNA Methylation**

Artificial intelligence (AI) has also demonstrated a significant promise in Alzheimer's disease (AD) diagnostics by the analysis of circulating cell-free DNA (cfDNA) methylation profiles. In one recent study, 3,684 CpG sites were identified that had significant differential methylation patterns between patients with AD and cognitively normal controls, pointing to epigenetic changes strongly associated with the pathology of the disease. To leverage these findings, six AI-based models were applied to cfDNA methylation data for diagnostic purposes. These models achieved impressive results, with Area Under the Curve (AUC) values ranging from 0.949 to 0.998. A deep learning model demonstrated particularly high performance, achieving an AUC of 0.99, with a sensitivity and specificity of 94.5% [34]. These metrics underline the great potential of AI in providing highly accurate, noninvasive diagnostic tools for AD.

- **Retinal imaging**

William Shakespeare once said, "The eyes are the window to your soul." Nowadays we can use our eyes as a window to our brain. The innermost layer of the eyeball called the retina originates from the middle part of the brain - the diencephalon. What is more, vessels of both structures share similar anatomic and physiological properties, and it is suggested that changes in retinal vasculature reflect changes in the cerebral vasculature [35].

Postmortem studies of patients affected by AD indicated specific retinal changes such as accumulation of Amyloid β peptide, vascular Amyloid β 40 and Amyloid β 42 deposits, pTau inclusion, gliosis, depletion of optic nerve ganglion cells, loss of nerve fiber layer and vascular damage [36,37,38]. As opposed to the cerebral vasculature, the retinal can be easily investigated in vivo at sub-cellular resolution, using methods such as Optical Coherence Tomography (OCT) and Optical Coherence Tomography Angiography (OCTA) [35,38].

OCT is a non-invasive imaging method that enables the visualization of the retina's layers as well as optic nerve fibers. Modification of this method is OCTA which additionally measures the size, shape, and blood flow of retinal capillaries without contrast agents. Both these methods are widely used in diagnosing glaucoma, age-related macular degeneration (AMD) and diabetic eye disease. Novel studies present their usability in diagnosing Alzheimer's disease [36]. In contrast to conventional AD diagnosis protocols, retinal imaging is simple, fast, inexpensive, and easily accessible.

AD patients' OCT and OCTA images present a significant decrease in vessel area and length densities in the inner vascular complexes (IVC), lower number of vascular bifurcations, decreased microvascular density and damaged vascular morphology in terms of VAD, VLD, and VB in the IVC when compared with controls [39].

Hao et al. have paired an innovative AI approach with more conventional biomarker analysis methods. They presented a novel interpretable graph-based deep learning model named Eye-AD, to identify early onset Alzheimer's disease (EOAD) and mild cognitive impairment (MCI) individuals through the unique characteristics of OCTA images. Their experimental results confirm that the Eye-AD model outperformed other approaches [40]. More studies are needed to establish the clinical role of OCT and OCTA in AD screening. Perhaps integrating other biomarkers (genetic information, cerebrospinal fluid markers, cognitive assessment) and AI in the future will help to build a comprehensive model to detect AD.

- **Genetic diagnostic**

The complex pathogenesis of AD has not yet been fully uncovered. Nevertheless, genetic mutations are well-established risk factors of AD, in fact, 60-80% of individuals with AD have genetic risk factors [41]. A significant role is assigned to mutations including the amyloid beta precursor protein (APP) gene, the genes for the presenilin 1 and presenilin 2 proteins, the genes for the ATP-binding cassette transporter protein 7 (ABCA7), and the genes related to Down's trisomy [42].

Single nucleotide polymorphism (SNP) is defined as a variation of a single nucleotide (adenine, thymine, cytosine, or guanine) in a DNA sequence [43]. It is the most common variation in the human genome and it can be used as a marker of a disease such as AD [44]. The apolipoprotein E protein gene (APOE) is also correlated to early onset of AD. The human APOE gene has three versions: APOE-ε2 (APOE2), APOE-ε3 (APOE3), and APOE-ε4 (APOE4), composed of several SNPs. These alleles vary in risk of developing AD. Individuals with APOE4 have a greater risk of developing AD, compared to homozygotes for APOE3. Surprisingly homozygotes for APOE2 have significantly reduced risk [45].

SNPs are proposed to be useful in detecting novel mutations linked to AD. Whole-genome sequencing obtained an enormous database of genetic information that now needs to be decoded and linked to specific disorders [46]. AI can process a massive amount of whole-genome data to recognize models of AD risk and progression [47]. Deep-learning model

presents a potential for multimodal data fusion, combining genetic information and neuroimage data (as a clinical manifestation of disease) to predict the AD stage [48]. That approach can uncover crucial mutations in AD pathogenesis and lead to the discovery of novel AD treatments, possibly stopping the disease progression.

2.3. Treatment

Current treatments for Alzheimer's disease aim only to manage its symptoms, and no effective methods for curing the disease have yet been established [49].
Effective management of Alzheimer's Disease depends on establishing shared goals and creating a collaborative partnership between the patient, caregiver, and healthcare provider.
Therefore, therapy must adopt a multidisciplinary approach, emphasizing both pharmacological and non-pharmacological strategies [50].

Pharmacological treatments for Alzheimer's disease include drugs that aim at slowing cognitive decline and those that address Behavioral and Psychological Symptoms of Dementia (BPSD) [51]. Cognitive decline mitigators authorized by The FDA include acetylcholinesterase inhibitors (ChEIs), which include donepezil, galantamine, and rivastigmine, and NMDA receptor antagonists, such as memantine [51,52]. The therapeutic efficacy of these anti-Alzheimer's drugs can be evaluated through tools like the Alzheimer's Disease Assessment-Cognitive Subscale and the Disability Assessment in Dementia (DAD) scale [52].

Cholinesterase inhibitors (ChEIs) enhance cholinergic activity by preventing the breakdown of acetylcholine in the synaptic cleft, aiding cognitive function in Alzheimer's disease (AD). They show small to medium efficacy in improving cognition, activities of daily living, and behavioral symptoms, with benefits demonstrated in short-term trials (24–52 weeks) and sustained over 2–4 years in long-term studies. ChEIs are generally well-tolerated, though they can cause mild gastrointestinal side effects and are contraindicated in conditions like severe cardiac disease or uncontrolled epilepsy [50,55].

Memantine is a moderate-affinity, non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that reduces excessive glutamate activation, a process implicated in neuronal excitotoxicity. It maintains the physiological role of glutamate in learning and memory while mitigating its detrimental effects [53]. Memantine acts by targeting the extrasynaptic NMDA receptor through a low-affinity, open-channel blocking mechanism, which inhibits neuronal damage resulting from excessive glutamate levels. This mechanism

contributes to its efficacy in attenuating neurotoxicity in Alzheimer's disease and other neurodegenerative disorders. Furthermore, memantine is commonly used in combination with acetylcholinesterase inhibitors for the management of Alzheimer's dementia, a combination that has been approved by the U.S. Food and Drug Administration (FDA) [56].

BPSD mitigators include medications approved by the FDA, such as brexpiprazole, an atypical antipsychotic that reduces agitation with minimal side effects, and suvorexant (Belsomra®), an orexin receptor antagonist used for managing sleep disturbances in individuals with mild-to-moderate Alzheimer's disease [51]. Recent trials have supported the use of citalopram (a selective serotonin reuptake inhibitor) and nabilone (a cannabinoid), which may also reduce agitation [57]. Additionally, risperidone is approved by the European Medicines Agency for short-term, 12-week use in dementia to treat severe agitation or psychosis that is resistant to other treatments [50]. Antipsychotics must be used with extreme caution under strict monitoring due to their black-box warning for dementia patients [54].

The predominant focus of the Alzheimer's disease drug development pipeline is on the advancement of disease-modifying therapeutic strategies. Such drugs include Aducanumab and Lecanemab, which target the underlying pathology of Alzheimer's by reducing Aβ burden and amyloid plaque accumulation [51,58].

Aducanumab (Aduhelm®), approved by the FDA in 2021, is the first pharmacological treatment for Alzheimer's disease to be FDA-approved that works by reducing Aβ burden [51,59]. Aducanumab is an IgG-1 monoclonal antibody that crosses the blood-brain barrier and selectively targets soluble oligomers and insoluble fibrillary Aβ plaques, slowing disease progression [60,61]. Approved for use in patients with mild cognitive impairment or mild Alzheimer's disease, it has no reported drug-drug interactions and can be used alongside other AD medications [51].

Lecanemab (Lequembi®) received accelerated FDA approval in January 2023. It is the second medication, following aducanumab, approved to target the disease's underlying pathophysiology in Alzheimer's treatment [51].

Lecanemab is a humanized monoclonal antibody that binds with high affinity to soluble Aβ-protofibrils, identified as neurotoxic agents. It decreases Aβ-fibril aggregation in astrocytes, leading to reduced amyloid plaque formation, clinical benefits, and disease modification [51,62].

A non-pharmacological approach to Alzheimer's disease is a key component of prevention and care strategies for individuals experiencing cognitive decline. These interventions focus on lifestyle adjustments and holistic measures that promote both physical

health and cognitive well-being. In 2019, the WHO issued its first guidelines on reducing the risk of cognitive decline and dementia, highlighting the importance of factors such as physical activity, a healthy diet, weight management, and controlling tobacco, alcohol use, hypertension, and diabetes [57]. Furthermore, supporting patients in recognizing and managing their emotional states is vital. This involves techniques such as physiotherapy to enhance motor abilities, environmental therapy to strengthen family dynamics and psychotherapy either individual or group sessions all of which contribute significantly to patient outcomes at every stage following diagnosis [63].

Addressing Alzheimer's disease requires a dual approach combining pharmacological treatments targeting symptoms and underlying pathologies with non-pharmacological interventions focusing on lifestyle, emotional well-being, and environmental support. This comprehensive strategy acknowledges that each patient's needs are unique, and integrating multiple therapeutic approaches offers the best chance for improved quality of life. As research progresses, disease-modifying therapies and innovative care models will likely shape the future of treatment and prevention.

3. CONCLUSIONS

This review examines the transformative role of artificial intelligence (AI) in advancing Alzheimer's disease (AD) diagnostics, highlighting its capabilities in early detection, risk assessment, and personalized treatment approaches. Across neuroimaging, genetics, and behavioral biomarkers, AI methodologies are demonstrating strong potential in identifying individuals at risk of transitioning from mild cognitive impairment (MCI) to AD.

AI-powered tools, such as those applied to FDG-PET imaging and cfDNA methylation analysis, show promise as non-invasive, highly sensitive, and accurate biomarkers. Similarly, technologies like optical coherence tomography (OCT) and OCT angiography (OCTA) combined with AI models like Eye-AD offer cost-effective and rapid diagnostic pathways for structural and microvascular changes associated with AD.

Moreover, AI's analysis of genetic data, including SNPs and whole-genome sequencing, is uncovering novel genetic risk factors and mechanisms underlying AD pathogenesis. When integrated with neuroimaging and behavioral biomarkers, these insights suggest opportunities for more comprehensive risk prediction and targeted interventions.

The findings from this review underscore AI's role as a key driver in reshaping AD diagnostics, enabling earlier detection, efficient diagnostic strategies, and personalized

treatment. These technological advancements not only aim to reduce the disease burden by allowing timely interventions but also provide a foundation for developing innovative therapeutic approaches, improving patient outcomes, and enhancing the quality of life for individuals affected by Alzheimer's disease and their caregivers.

4. DISCLOSURE

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