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Artificial Intelligence and Alzheimer's Disease: Bridging Complexity with Precision Medicine

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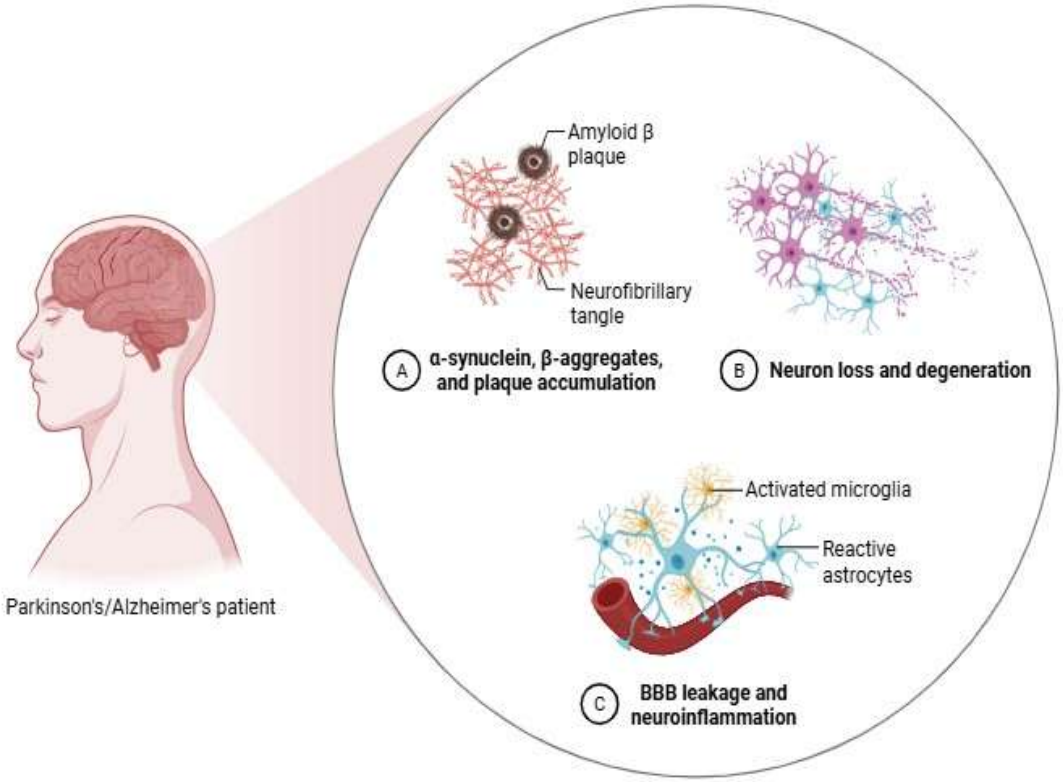
Abstract

The most prevalent cause of dementia and a progressive neurodegenerative illness, Alzheimer's disease (AD) has a substantial negative impact on both global health and the economy. There is presently no cure, despite much study, and treatments like memantine and cholinesterase inhibitors just alleviate symptoms. The multifaceted character of AD, comprising intricate genetic, epigenetic, and environmental connections, has been brought to light by developments in genomics, neuroimaging, and clinical data. Novel computational techniques are necessary since traditional methods often fail to understand such high-dimensional information. In AD research, artificial intelligence (AI), especially machine learning and deep learning, has become a game-changing tool. In order to enable early diagnosis, prognosis, biomarker identification, and therapy development, artificial intelligence (AI) makes it easier to analyze large datasets from next-generation sequencing (NGS), transcriptomics, proteomics, imaging, and genome-wide association studies (GWAS). AI applications in AD include determining transcriptomic and epigenetic biomarkers, discovering new gene-gene interactions, connecting neuroimaging indicators with genetic differences, and predicting disease risk using genetic risk scores. Furthermore, by combining multifaceted biological and clinical data, AI-driven methods facilitate drug discovery, repurposing, and clinical trial optimization. Recent research highlights AI's promise in precision medicine for AD by showing that it can combine genetic, imaging, and biomarker data to reach high prediction accuracy. Nonetheless, there are still issues with clinical validation, data heterogeneity, and interpretability. The uses of AI in deciphering the genetics and pathophysiology of AD are highlighted in this study, along with current advancements and constraints. It also offers insights into potential future paths where AI might speed up the conversion of complicated data into useful methods for AD diagnosis and therapy.

1. Introduction

Dementia worsens with time in Alzheimer's disease (AD), a neurodegenerative condition that ultimately causes individuals to lose their capacity to react to their surroundings. There is presently no cure for AD, with the exception of memantine and cholinesterase inhibitors, which may temporarily reduce or stabilize symptoms [1]. As the world's population ages, AD becomes a significant societal burden in addition to causing greater

personal and familial pain. It also increases the incidence of anxiety and despair among those who care for AD patients [2]. According to estimates, 10% of Americans 65 and over now have AD. In the United States, there were over 5.8 million AD patients in 2019. This figure might rise to an estimated 13.8 million in the United States by 2050, while the global dementia population is expected to reach 131.5 million [3-5]. AD is divided into two categories based on the age at which it first manifests: early-onset AD (EOAD) and late-onset AD (LOAD). Approximately 5% of all AD cases are EOAD, which affects people under 65. Less than half of these individuals have early-onset familial AD, a causative mutation that shows up as an autosomal dominant inheritance pattern. Patients over 65 are at risk for LOAD, which makes up around 95% of all AD cases. AD may also be separated into familial and sporadic instances based on the presence of family aggregation. Although EOAD is more common in familial situations, LOAD is also present. Over 90% of individuals with AD are sporadic instances, most of whom also have LOAD [6].



Although an estimated 70% of the risk is due to hereditary factors [9–12], the etiology for the majority of AD cases is still unknown and is believed to be the consequence of a complex interplay between genetic and environmental variables engaged in neuronal and immunological processes [7, 8]. The amyloid hypothesis is now a widely accepted idea regarding the etiology of AD. Although the precise pathological process is unknown, this theory contends that a number of factors lead to an imbalance in the production and clearance of β-amyloid, which causes β-amyloid to accumulate in the brain. This accumulation causes neuroinflammation and neurofibrillary tangles to form in neurons, which ultimately cause neuronal dysfunction and death [13].

Finding the genetic and environmental causes of illness, or etiology studies, is one of the main objectives of medical research. The findings of these studies may provide hints for future study on AD prevention and therapy. Newton's technique, which stresses that the world's seeming complexity can be resolved by studying events and breaking them down into their most basic components, has been extensively used in scientific research since the 17th century, including medical research. In reality, by using this practice, we have had tremendous success. Many illnesses caused by one or more causes have been effectively prevented and treated in the medical sector. For instance, because to vaccinations, smallpox has been eradicated worldwide. Unfortunately, there are currently no effective preventative or reversible treatment options for some complex diseases, like AD, primarily because these conditions entail intricate interactions between numerous variables, and human complexity precludes the use of a simplified model to comprehend these conditions [14, 15]. These issues involving vast amounts of data and very complex structures that are beyond the human brain's processing capacity may now be resolved because to the quick advancement of artificial intelligence (AI) technology in

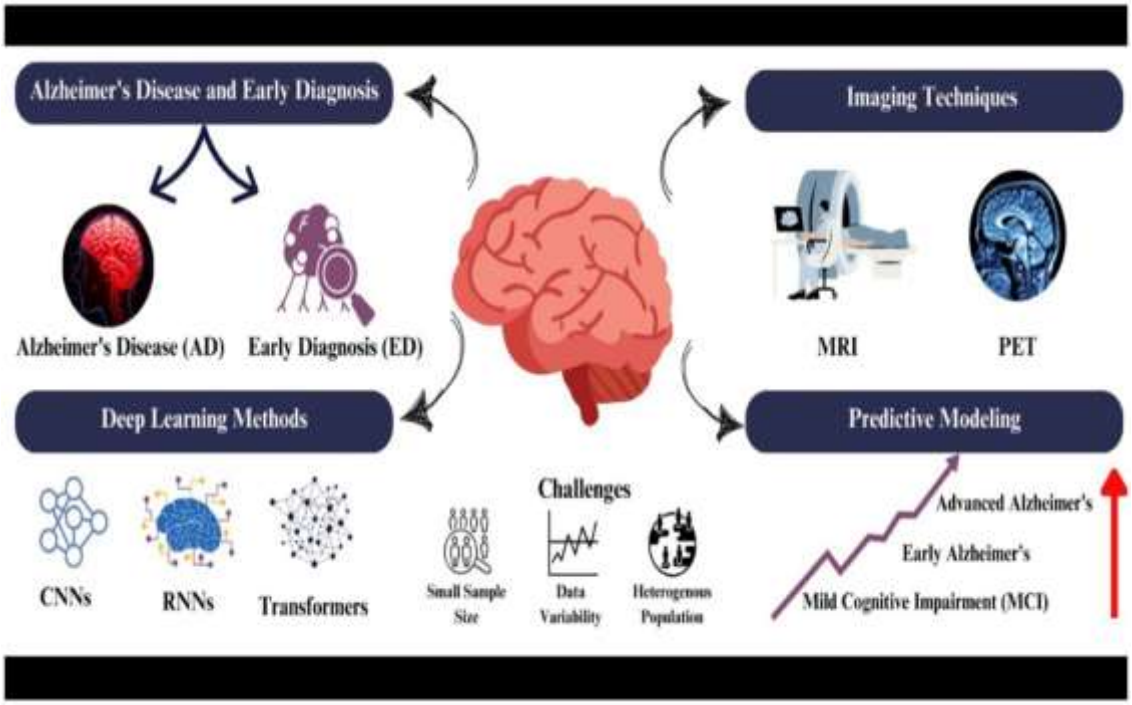
recent years [16–18]. In terms of the quantity of AI research done, AD came in fourth place out of all disorders [19]. The phenomenology of neuropsychiatric illnesses is influenced by complex, social dynamics, and AI takes an integrative approach, modeling neurobiological components as functional modules of pathology [20]. Research on AD pathogenesis has focused on genetic variables since they are the primary cause of the majority of AD cases. Research involving genetic data has grown rapidly in recent years due to the widespread use of next-generation sequencing and microarray technologies. AI technology is desperately needed in this circumstance. AI-powered genetic research on AD is now expanding steadily. As a result, the research in this area has been thoroughly reviewed in this article, which also offers an outlook on the future course of advancements.

2. Artificial Intelligence

One may argue that using tools is a natural "extension" of the human body's capabilities. Similarly, computers may work as "extensions" of the human brain. AI has or almost "will surpass human performance in several domains" due to the rapid expansion of computer power, the collection of vast quantities of data, and the theory of computation [21, 22]. Humanity's most valuable asset for surviving on Earth has been and continues to be intelligence. There is cause for optimism that human productivity will usher in a new age as AI technology advances. There are numerous definitions of artificial intelligence (AI) from various angles, but the most widely accepted ones are as follows: AI is a field of computer science that makes it possible for computers to carry out tasks that typically require human intelligence; another definition is that AI is a system that senses its surroundings and acts in a way that maximizes the likelihood of finishing a task [23]. Numerous algorithms, techniques, or strategies have been devised to accomplish "intelligent" operations. The primary ways of AI technology include learning from examples, knowledge-based reasoning and planning, searching for solutions to problems, and uncertain knowledge-based reasoning. Uninformed or heuristic searches, local searches, optimizations, evolutionary computations, and adversarial searches are some of the techniques or tactics for addressing problems via searching. Logic programming, automated reasoning, and ontological engineering are examples of knowledge-based planning and reasoning. Bayesian networks, hidden Markov models, Kalman filters, a utility theory, and decision networks are examples of uncertain knowledge-based reasoning. Machine learning and mathematical/statistical categorization are the foundations of learning from instances. The most popular AI method among them in both academia and business is machine learning [24, 25].

The goal of machine learning, a branch of artificial intelligence, is to create computer programs that become better on their own with practice. It analyzes the data and finds patterns in it to deal with datasets. The two main types of machine learning techniques are supervised and unsupervised learning algorithms. Supervised learning algorithms work best for classification and regression problems because they employ labeled data, or training data that yields the right answer when given an input. Artificial neural networks, Bayesian networks, support vector machines, decision trees, random forests, and K-nearest neighbors are examples of prevalent algorithms. Unsupervised learning algorithms, on the other hand, work with unlabeled data and must identify and understand innate patterns in the collection. K-means, distance clustering, density clustering, hierarchical clustering, and Markov chain are examples of popular methods. Additionally, certain algorithms—like reinforcement learning—combine supervised and unsupervised learning [24, 26, 27].

An even more specialized subset of AI and machine learning is called deep learning. One kind of machine learning algorithm that mimics how the human brain solves issues is called deep learning. It is made up of many "layers," each of which has a different number of nodes that are all linked in a network. When data enters the first "layer," it undergoes a number of linear modifications before finally producing a result. Depending on how it is used, it may be enhanced, monitored, or unsupervised [28]. Prior to artificial intelligence, a lot of projects were carried out using intricate rule-based algorithms that only became more complex as more data anomalies were found. To attempt to account for every potential quirk, we can keep adding rules and algorithms, but this is time-consuming and difficult. But these patterns can be easily learned by a machine learning application. Additionally, machine learning will be able to find more complicated or abstract patterns included in the data. The ability of a computer to recognize patterns and logic in data improves with increasing data amount, quality, and diversity. The new methods for gathering vast volumes of biological data, such genomic and other omics biology information, make this data explosion particularly apparent in the medical field [29]. As a result, AI will play a significant role in healthcare applications such as illness prevention, detection, diagnosis, and treatment, health system management, and medical research development [30-33].



3. AI's Use in Medicine

The development of AI technology in clinical medicine, health systems management, public health, and medical research is now being undertaken by several IT businesses and academic organizations. In clinical medicine, advances in computer vision, image and video analysis, and artificial intelligence (AI) have greatly enhanced picture recognition and categorization, which is very advantageous for medical imaging. These technologies have shown excellent outcomes in several areas and have been created for imaging diagnosis in radiology [34], pathology [35], dermatology [36], ophthalmology [37], cardiology [38], neurology [39], gastrointestinal [40], and surgery [41]. Additionally, by learning the health trajectory from a large number of individuals, AI can forecast the course of illness and the impact of therapy. For example, a deep learning system for the early prediction of AD was built using 18F-fluorodeoxyglucose PET of the brain, and it obtained 82% specificity and 100% sensitivity at an average of 75.8 months before the final diagnosis [42]. As a result, it is thought that using AI technology in clinical settings might enhance the standard of medical care, which would be especially beneficial for doctors who lack education or experience, particularly in underdeveloped nations with limited access to healthcare resources [43]. AI may also increase access to healthcare services; for instance, patients can utilize self-care apps on their smartphones or smart watches, some of which have FDA approval. Precision medicine is customized to the patient's individual healthcare plan and clinical choices, taking into account the patient's genetics, surroundings, and lifestyle. Large volumes of genetic, environmental, and lifestyle data may be analyzed and processed by AI technology, enabling the use of precision medicine in clinical settings. Furthermore, it could be crucial for public health and health system management [17, 27, 30, 44-46].

Genomes, transcriptomes, proteomics, cytological images, chemical and biological macromolecular structures, interaction information, and clinical data from electronic medical records are just a few examples of the complex biological processes from which a vast amount of laboratory and clinical research data can be extracted using currently available biological and medical technologies in the field of biomedical research. AI technology may aid in the creation and screening of therapeutic compounds, as well as the design and analysis of clinical trials, by analyzing and processing huge and complicated biological data to help elucidate the corresponding physiological and pathological pathways. Predicting the binding affinities of transcription factors, DNA- and RNA-binding proteins, cis-regulatory/enhancer elements, DNA methylation sites, histone modifications, chromatin accessibility, transcription start sites, tissue-regulated splicing, unique gene expression and translation efficacies, transcriptome patterns in a given cell or condition, microRNA precursors and binding targets, variant calling, functional consequences of noncoding variants, and pathogenicity of coding variants are all ways that artificial intelligence can assist gene-level research. AI may also be used to create protein-coding DNA sequences, detect long noncoding RNAs, and create DNA probes for protein binding microarrays. Deep learning seems to be the most effective method for analyzing various data sources

and finishing genomic modeling jobs as the quantity of genomic data increases rapidly; yet, the prediction of complex human disease phenotypes is still far from being developed [47–50]. The secondary structure, solvent-accessible surface area, protein contact maps, and disordered areas may all be predicted by current AI technologies for protein level study; nevertheless, tertiary protein structure prediction remains difficult [51, 52]. Automated high-content, high-throughput imaging technology is a valuable tool for examining biological concerns at the cell and tissue level. It may also be employed at any stage of the development of target-based therapies. Signal denoising and enhancement, segmentation, label-less imaging, live cell imaging, imaging-based phenotypic, single cell tracking, and modeling of rebuilt pedigree trees are some of the specific tasks that artificial intelligence does in image processing [53, 54]. The creation of novel medications may be significantly accelerated with the use of AI technologies in the chip laboratory, cell-based or organoid-based tests, and autonomous chemical synthesis. AI may be used to evaluate high-throughput compound screening data and literature, as well as to suggest strategies for automated chemical synthesis and preliminary molecular screening. Following the acquisition of bioassay data, a new molecular optimization strategy may be suggested and the bioassay can be conducted once again by upgrading the machine learning model. Thus, a high-throughput bioassay and AI design-based automated drug development cycle is created [55]. One quick and inexpensive method of medication development is drug repurposing. By examining extensive transcriptomics, molecular structural data, and clinical databases, artificial intelligence (AI) can forecast medication repurposing [56]. Researchers think that using AI technology in the planning and execution of clinical trials might assist address the issue of clinical trials being the bottleneck of new medication development. AI may assist in the selection of a subset of the population that may be susceptible to novel medications by evaluating clinical and genetic data from patients. It can also assist in the recruitment of participants by connecting them with clinical trials. A mobile, real-time patient monitoring system and the ability to anticipate a patient's dropout risk may be obtained by combining AI technology with wearable sensors and noninvasive diagnostics during clinical trials [57]. There aren't many instances of clinical applications, despite the fact that research on AI-based medical technology has advanced quickly and has many potential uses. One may argue that medical technology based on AI is still in its early stages [30, 58].

4. Genetics Research

According to estimates, genetic variables may account for around 70% of the etiologic role in AD cases other than early-onset familial AD [9, 10]. Single nucleotide variations (SNVs), tandem repeat variations, small insertions and deletions, large segment deletions and duplications (copy number variations), chromosome rearrangements (duplication, deletion, inversion, and translocation), and aneuploidy or polyploidy (often leading to major genetic diseases) are among the genetic variations among individuals in the population [59]. The noncoding portion of the human genome makes up around 99 percent of its total size, which is about 3.2 × 109 base pairs (bp). Along with producing transfer RNA, ribosomal RNA, and microRNAs, the noncoding region also contains regulatory elements (promoters, enhancers, silencers, and insulators); long noncoding RNAs; and chromosome structural elements like satellite DNA and telomeres [50, 60, 61]. Four methods have been used to find genetic variations linked to the onset of AD in the human genome: next-generation sequencing (NGS)-based association studies, genome-wide association studies (GWAS), candidate gene/pathway association studies, and genetic linkage analyses [62].

One of the first methods for determining the genetic foundation of Mendelian characteristics was genetic linkage analysis. Using genetic markers and segregation analysis in pedigrees, it maps genetic loci [63]. Early-onset familial AD was identified by genetic linkage analysis to include causative mutations in three genes: amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) [57]. Accordingly, they are found on chromosomes 1, 14, and 21 [64]. The pathological alterations of EOAD are caused by an additional copy of chromosome 21 that is carried by people with Down syndrome [65].

Small-scale, low-resolution association studies based on what is known about certain genes are known as candidate gene/pathway techniques. Alleles of the apolipoprotein E gene (APOE) have been shown to be risk factors for late-onset AD using this method. Despite its lack of usage nowadays, this approach may still be useful depending on the gene or population, for as when examining polymorphisms with low allele frequencies [66,67].

GWAS may evaluate the relationship between hundreds of single nucleotide polymorphisms (SNPs) of a disease and provide data on genetic variants linked to the risk of certain illnesses, thanks to advancements in microarray technology [68]. Large GWAS samples of LOADs including tens of thousands of patients have been carried out by certain international cooperation initiatives, such as the International Alzheimer's Disease Project (IGAP) [69, 70].

All of the genetic variants mentioned above, with the exception of APOE, have little impact on the pathophysiology of AD. It may be required to take into account the impact of many variations (additive effects), epistasis (multiplicative effects), and the interaction of genes with the environment in order to comprehend the etiology of AD other than early-onset familial AD. By counting the number of disease-related alleles and their ability to predict AD risk, genetic risk scores may be used to characterize the combined impact of many variations on the pathophysiology of AD. The highest prediction accuracy for AD was 82%, according to a genetic risk score research based on an SNP dataset including 1,554 controls and 3,049 AD patients [83]. While individual gene analyses revealed no impact, interactions were discovered in certain genes that had never before been linked to AD in epistasis investigations, such as the interacting SNP pair in KHDRBS2 and CRYL1 [84]. The findings provide evidence that the epistasis effect has a role in some of the hereditary components of AD. Research on gene-to-gene interactions in AD is compiled in a review paper by Raghavan and Tosto [85]. Functional genomics aims to provide a complete explanation of the intricate relationship between genotypes and phenotypes by connecting omics data from transcriptomics, proteomics, metabolomics, and genomes. APP metabolism, inflammation, lipid metabolism, tau protein binding, endocytic/vesicular-mediated transport, and synaptic function pathways were the primary areas of enrichment for AD-related genetic variations, according to functional pathway analysis [11, 62, 70, 71, 86].

Numerous environmental factors, such as brain trauma, low educational attainment, cardiovascular disease risk factors, lifestyle choices (such as smoking, drinking, exercising, and being around greenery), air pollution [88], exposure to heavy metals (such as manganese and mercury) [89, 90], pesticide exposure, etc., have been found to raise the risk of AD. It is hypothesized that these environmental risk factors may initiate the pathogenesis of AD by interacting with an individual's risk genes, but there is no proof that they are the only cause of AD. Research has assessed how APOE genes interact with their surroundings. For instance, people who have poor physical activity and the APOE ε4 allele are much more likely to acquire dementia than those who have only one of these factors [91]. The relationship between genetic variants and environmental risk factors, however, has received very little study attention [92].

The contribution of mitochondrial genetic diversity to AD risk is equivocal because of the limited sample size and lack of confirmation, despite reports suggesting certain mitochondrial haplogroups and single nucleotide polymorphisms influence the risk of AD [95, 96].

Method	Focus/Approach	Key Findings	Significance in AD	References
Genetic Linkage Analysis	Pedigree-based mapping using genetic markers	Identified mutations in APP, PSEN1, PSEN2 linked to EOAD; extra copy of chromosome 21 in Down's syndrome causes AD-like pathology	Established the first causal genes in AD	[57], [63–65]
Candidate Gene/Pathway Studies	Focused on pre-selected genes/pathways	APOE ε4 allele identified as strongest genetic risk factor for LOAD	Still useful in rare allele studies, especially in specific populations	[66,67]
Genome-Wide Association Studies (GWAS)	Screening thousands of SNPs across large cohorts	Identified risk genes including APOE, BIN1, PICALM, SORL1, CLU	Expanded knowledge of polygenic risk factors	[68–70]
Next-Generation Sequencing (NGS)	High-throughput DNA sequencing	Revealed rare and low-frequency variants influencing AD risk	Enables discovery beyond common SNPs	[62]
Genetic Risk Scores (GRS)	Combining multiple SNPs into predictive score	Prediction accuracy up to 82% (study with 1,554 controls & 3,049 AD patients)	Useful for risk stratification and precision medicine	[83]
Epistasis (Gene–Gene Interactions)	Interaction studies (Bayesian networks, combinatorial epistasis learning)	Discovered novel SNP–SNP interactions (e.g., KHDRBS2–CRYL1)	Reveals hidden complexity beyond single-gene studies	[84,85]
Functional Genomics / Pathway Analysis	Integrating transcriptomics, proteomics, metabolomics with genetics	Enriched pathways: APP metabolism, tau binding, inflammation, lipid metabolism, synaptic function	Bridges genotype–phenotype gap	[11,62,70,71,86]

Gene–Environment Interaction Studies	Examining lifestyle/environment with genetic risk	APOE ε4 + low physical activity strongly ↑ dementia risk	Supports multifactorial model of AD	[88–92]
Epigenetic Studies	DNA methylation, histone modifications, ncRNAs	Altered methylation (e.g., APOE CpG, HOXA cluster), abnormal HDAC activity, deregulated miRNAs/lncRNAs	Shows regulatory changes beyond DNA sequence	[62,93,94]

5. The Use of AI in Genetic Analysis of AD

Large data analysis of high-dimensional complex systems has shown the effectiveness of AI technologies, particularly machine learning techniques. Currently, genetic variants, gene expression profiles, gene-gene interactions in AD, genetic analyses of AD based on a knowledge base, and genetic data-based diagnostic and prognosis studies have all made use of machine learning.

5.1. The prognosis and diagnosis

Previously, by examining patient genetic data, AI algorithms were utilized to predict the diagnosis and prognosis of AD. Two studies of centenarians and other AD and Parkinson's disease patients in Japan were published by Takasaki et al. in 2008 and 2009.

In the first study, they analyzed mitochondrial single nucleotide polymorphisms (mtSNPs) at certain places in mitochondrial DNA using a radial basis function (RBF) network. They discovered that various subject types had distinct mtSNPs. The G2a haplogroup is strongly associated to AD patients from Japan. The second study demonstrated that Japanese AD patients were linked to the B4c1 and N9b1 haplogroups in addition to the G2a haplotype. According to the authors, this analytic approach may be used for the first diagnosis in order to forecast the likelihood that an individual would acquire AD or a number of other disorders [83,84]. With 312 to 318 SNPs in 1,411 patients, Wei et al. (2011) created a model-averaged naïve Bayes (MANB) model that outperforms earlier models in predicting LOAD patients. The receiver operating characteristic curve's (AUC) area under the curve was 0.72. Furthermore, using high-dimensional genomic data for training and testing improves the model's performance. The findings provide evidence that AD may be predicted from genome-wide data using MANB [85].

A support vector machine (SVM) technique was developed by Xu et al. in a recent research to examine gene-encoded protein sequences rather than patient genotype data. The algorithm's prediction accuracy was 85.7% when evaluated using 1,463 non-AD-related data and 279 AD-related protein sequence data from the UniProt database. This study's flaw, however, is that it fails to differentiate between early-onset familial AD and other forms of AD based on protein sequence information [86]. In order to create a gene coexpression network and find potential AD diagnostic biomarkers, Wang et al. also used the SVM classifier to examine the microarray gene expression dataset from the NCBI GEO database (www.ncbi.nlm.nih.gov/geo). A group of 44 genes were shown to be possible biomarkers [87].

In order to identify patients with mild cognitive impairment (MCI) who will develop AD within three years, Varatharajah et al. developed a multivariate model based on machine learning algorithms (SVM, multiple kernel learning). This model integrates demographics, biomarkers of cerebrospinal fluid (CSF), magnetic resonance imaging (MRI), positron emission tomography (PET), a psychological test score for cognition and cognitive resilience, and the top AD-related genes that have been validated (including 94 potential predictive factors). They achieved an astounding 93% prediction accuracy rate by examining 135 ADNI subjects [88]. According to the aforementioned study, there is some benefit in using machine learning techniques to analyze genetic data in order to predict the prognosis and risk stratification of AD; however, its accuracy will be significantly increased if imaging data is also included.

5.2. Examination of genetic differences in AD

As brain imaging technology has advanced, it has been shown that certain structural and functional changes in the brain may take place years before AD is diagnosed [89]. Neuroimaging genetics is the field of study that examines the relationship between genetic differences and changes in brain imaging. One of the most significant resources for sharing AD brain imaging data is the ADNI project, which has been tracking and gathering clinical, imaging, genetic, and biochemical biomarker data for AD patients since 2004. The project is funded by the US National Institutes of Health and pharmaceutical companies.

The multivariate relationships between many SNPs and neuroimaging features may be found using sparse canonical correlation analysis (SCCA). In order to examine the relationships between genetic markers found in the APOE gene and MRI and amyloid imaging data obtained from the ADNI database, Du et al. developed two structural SCCA models. They discovered a substantial correlation between amyloid load in the frontal area and damage to the right hippocampal region and the APOE ε4 allele rs429358 [90,91]. Hou et colleagues. discovered many risk genetic variations of AD linked to the APOE, BCR, NPC2, and RFTN1 genes by performing regression analysis on SNP and MRI datasets of ADNI using a multitask learning model [92].
The pathophysiology of AD may include particular genes that are tissue-specific. The network wide association study (NetWAS) approach may prioritize GWAS analysis by using machine learning techniques to tissue-specific functional interaction networks. The protocadherin alpha gene cluster (PCDHA) may be a suspect gene, according to Song et al.'s analysis of the ADNI GWAS dataset using the hippocampus volume as the phenotype [93]. Without taking into account the dynamics of phenotypic changes, the aforementioned research examined the relationship between genetic variants and static neuroimaging phenotypes at a particular time point. The dynamic neurodegenerative process may be explained by these shifting phenotypes, according to Hao et al.'s hypothesis. They developed a "temporally constrained group sparse canonical correlation analysis framework" that was trained using time series data from the ADNI database. The impact of the risk locus rs429358 on the decline of AD was questioned by the longitudinal method, but they also concentrated on SNPs close to the APOE gene and discovered that this model could detect stronger associations than previous SCCA models, confirming that the loci rs76692773 and rs2075649 were top ranking [94].

5.3. Examination of the AD Gene Expression Profile

Gene expression patterns in brain cells may be changed by genetic variants alone or in conjunction with environmental influences. This can result in anomalies in the metabolism of certain proteins and eventually cause pathogenic alterations in AD. In order to identify important genes and pathways linked to the pathophysiology of AD, which may be targets for therapeutic intervention, it is useful to investigate variations in gene expression levels in brain cells. RNA-sequencing (RNA-Seq) based on next-generation sequencing technology and high-throughput microarray may provide a thorough snapshot of the transcriptome of cell or tissue samples. They are unable to learn much about the biological mechanisms of a particular illness because of the great dimensionality and complexity of the data. In order to successfully expose complicated biological traits, several research have switched from conventional statistical approaches to machine learning methods for data analysis.
More complex methods have been utilized in recent studies, and many of these experts think that in order to identify any more genes involved in AD, unusual and complex algorithms should be used. Martinez-Ballesteros et al. trained on many meticulously constructed gene expression datasets by combining decision tree classifiers, quantitative rules, and hierarchical clustering techniques. To corroborate their findings, they did, however, also take into account other sources, such as a gene ontology, a library of previously relevant AD genes, a literature study, or expert knowledge. They discovered that 90 genes had substantially altered expression in AD patients compared to controls [95].

5.4. gene-gene interactions

Gene-gene interactions have important roles in the pathophysiology of AD, as was previously established. Studies of metabolic pathways, transcript interaction networks, and SNP epistatic interactions have all made use of machine learning methods. Jiang and colleagues (2011) developed a Bayesian network-based combinatorial epistasis learning technique. This strategy is possible, according to their evaluation of its performance with various settings on simulated datasets and a genuine Alzheimer's GWAS dataset [96]. Jiang et al. later enhanced the technique by combining information gain and Bayesian network techniques. A GWAS LOAD dataset of 552 control cases and 859 AD was examined by them. The findings showed additional interactions, such as APOE / GAB2 interactions involving more loci, in addition to being in line with earlier data [97]. Using the same GWAS LOAD dataset as Jiang et al., Han et al. also used a Bayesian network-based technique to identify epistatic interactions. Their discovery of two SNPs (rs1931565 and rs4505578) may raise the risk of LOAD due to their interactions with APOE [98].
Iterative sure independence screening (SIS), another machine learning approach, is capable of analyzing extremely big datasets with more predictors than observations. Hibar et al. conducted an interaction study, screening 534,033 SNPs in a GWAS dataset from ADNI for any potential SNP-SNP interactions that impacted regional brain sizes. 1.9% of the variations in the temporal lobe volume might be explained by a substantial SNP-SNP interaction they discovered between rs1345203 (likely linked to histone acetylation) and rs1213205 (likely related to DNase I cleavage) [99].

Numerous research have also examined transcript interaction networks utilizing machine learning techniques. In a previous research, Armananzas et al. constructed transcript interaction networks using ensemble Bayesian network classifiers based on transcript profiling from samples of the dentate gyrus and entorhinal cortex in six AD and six control patients in 2012. According to research, a few critical transcripts in the network, including S100A10, RPS3A, and MED8, may be crucial for the pathophysiology of AD [100].

5.5. Using a Knowledge Base for Genetic Analysis

The majority of research that used machine learning to understand the pathophysiology of AD examined genetic or other medical data (such brain imaging) from different original AD datasets. Few research, nonetheless, are searching for other approaches to support its growth. These investigations used an existing biological knowledge base using AI technology to find genes linked to AD risk.

Jamal et al. used eleven machine learning algorithms to examine many open-source knowledge sets in an attempt to identify genes that are prone to AD. The sequence features (UniProt database), functional annotations (DAVID and two additional Swiss-Prot functional annotation terms), and protein-protein interaction networks (OPID, STRING, MINT, BIND, and InTAct databases) were used to extract the integrated topological properties of the AD-related genes. Additionally, they screened interactions between newly discovered AD-related proteins and recognized AD medications using molecular docking techniques [101]. Furthermore, Huang et al. integrated the data from a brain-specific gene network from GIANT and an AD gene knowledge base (AlzGene) using an SVM algorithm. They then examined over 20,000 genes in a catalog of human genes and genetic diseases (OMIM). The 832 candidate genes produced in this analysis may serve as a thorough reference for AD gene research [102]. The task of searching the literature may be aided by text mining techniques. A machine learning technique that may automatically extract disease-gene-variation information from biomedical literature was suggested by Singhal et al. From every PubMed abstract, they retrieved the aforementioned data for 10 significant illnesses, including AD. The author concluded that the strategy had practical utility after comparing it to the UniProt knowledge base [104].

Dataset / Input	AI / ML Method	Key Findings	References
Mitochondrial SNPs in Japanese AD, PD, centenarians	Radial Basis Function (RBF) Network	Identified haplogroups G2a, B4c1, N9b1 associated with AD in Japanese patients	[99,100]
312–318 SNPs in 1,411 patients	Model-Averaged Naïve Bayes (MANB)	Achieved AUC 0.72, outperforming earlier models	[101]
Protein sequence data (279 AD-related vs 1,463 non-AD)	Support Vector Machine (SVM)	85.7% accuracy in distinguishing AD-related proteins	[102]
Microarray gene expression (NCBI GEO)	SVM Classifier	Identified 44 potential gene biomarkers for AD	[103]
Multimodal data (CSF biomarkers, MRI, PET, genetics, cognition) in 135 ADNI subjects	SVM + Multiple Kernel Learning	Predicted MCI-to-AD conversion with 93% accuracy	[104]
AD case-control dataset (380,157 SNPs)	Decision Tree + Random Forest	Stratified SNPs into relevant subgroups	[103]
AD & PD GWAS datasets	Improved Random Forest (2-stage sampling)	Outperformed conventional SNP selection methods	[104]
ADNI neuroimaging + GWAS data	Sparse Multimodal Multitasking Learning	Identified APOE, BIN1, PICALM, SORL1, IL1B as biomarkers	[99]
ADNI MRI + amyloid imaging + SNPs	Sparse Canonical Correlation Analysis (SCCA)	Linked APOE ε4 (rs429358) with amyloid load & hippocampal atrophy	[100]
ADNI SNP + MRI dataset	Multitask Learning Regression	Found risk variants in APOE, BCR, NPC2, RFTN1	[101]
ADNI GWAS + hippocampal volume phenotype	NetWAS (network-wide association study)	Identified PCDHA gene cluster as AD-related	[102]
ADNI longitudinal SNP + imaging data	Temporally Constrained Group SCCA	Confirmed APOE locus; identified rs76692773, rs2075649	[103]
WGS + imaging (6M SNPs, hippocampal/entorhinal volumes)	Lasso Regression, Structured Sparse Regression	Identified novel genes: VAT1L, CACNA1C, FGF14, BACE2, etc.	[104]

Future Scope

Research on Alzheimer's disease (AD) might revolutionize diagnostic, prognosis, and treatment approaches by using artificial intelligence (AI). A more comprehensive knowledge of AD pathogenesis will be possible in the future because to AI-driven multimodal data integration that combines genomes, neuroimaging, proteomics, metabolomics, and electronic health records. New biomarkers for early and even pre-symptomatic identification may be found as a result of this integration, allowing for prompt intervention. Furthermore, in

order to convert computational results into clinically useful insights and improve patient care and physician trust, explainable AI models will be essential.

When combined with AI-based analytics, wearable technology and Internet of Things (IoT) devices may provide ongoing, real-time monitoring of behavioral and cognitive changes in those at risk for AD. Novel treatments will be found more quickly thanks to AI-guided drug discovery and repurposing, and adaptive algorithms may improve patient classification, recruitment, and clinical trial design. AI-powered personalized medicine techniques might aid in creating individualized treatment plans based on a patient's genetic and lifestyle characteristics.

Addressing the issues of data heterogeneity, interpretability, and ethical concerns will need cooperation between computer scientists, neuroscientists, and physicians. All things considered, AI is expected to be crucial in advancing AD research from descriptive to predictive, preventative, and precision medical treatments.

Conclusion

Alzheimer's disease remains one of the most pressing medical challenges of the 21st century, with its complex interplay of genetic, environmental, and epigenetic factors making prevention and treatment extremely difficult. Conventional research methods, while valuable, are often limited in their ability to process and interpret the vast volumes of multidimensional data generated by modern biomedical technologies. Artificial intelligence (AI) offers a transformative solution by enabling high-throughput analysis, pattern recognition, and predictive modeling across genetic, transcriptomic, imaging, and clinical datasets.

AI applications in AD have already demonstrated remarkable potential in identifying genetic variants, uncovering gene-gene and gene-environment interactions, linking neuroimaging signatures to disease progression, and predicting risk with improved accuracy. Moreover, AI-driven approaches are accelerating drug discovery, repurposing, and clinical trial optimization, thereby addressing critical bottlenecks in therapeutic development. While challenges such as data heterogeneity, lack of standardization, interpretability, and ethical considerations remain, ongoing advancements in explainable AI and collaborative research are steadily overcoming these barriers.

In summary, AI is poised to revolutionize the landscape of Alzheimer's disease research and clinical care. By enabling precision medicine, facilitating early detection, and guiding personalized therapeutic strategies, AI not only enhances our understanding of AD pathogenesis but also holds the promise of reshaping its management and improving patient outcomes in the years to come.

References

1. Chen X, Zhang X, Li X, Zhao Y, Yang L, Wang Y, et al. Recent advances in the diagnosis and treatment of Alzheimer's disease. Front Genet. 2023;14:1138270.
2. Jeong S. Molecular and cellular basis of neurodegeneration in Alzheimer's disease. Mol Cells. 2017;40(9):613–20.
3. Mudher A, Lovestone S. Alzheimer's disease—do tauists and baptists finally shake hands? Trends Neurosci. 2002;25(1):22–6.
4. Liu YH, Giunta B, Zhou HD, Tan J, Wang YJ. Immunotherapy for Alzheimer's disease. Biomed Pharmacother. 2011;65(7):539–46.
5. Pujari R, Vyawahare N. Alzheimer's disease: future drug development strategies. Int J Pharm Sci Rev Res. 2014;29(2):138–47.
6. Murphy MP, Levine H. Alzheimer's disease and the amyloid-beta peptide. J Alzheimers Dis. 2010;19(1):311–23.
7. Chen C, Guo T, Wang J, Guo H, Zhang C, Zhang L, et al. Research progress of Alzheimer's disease detection technology based on nano-biosensing. Front Aging Neurosci. 2023;15:1181815.
8. Jeong S. Molecular and cellular basis of neurodegeneration in Alzheimer's disease. Mol Cells. 2017;40(9):613–20.
9. Karran E, Mercken M, De Strooper B. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. Nat Rev Drug Discov. 2011;10(9):698–712.
10. Yu W, Lu B. Synapses and dendritic spines as pathogenic targets in Alzheimer's disease. Neural Plast. 2012;2012:247150.
11. Nasr P, Gopalkrishna S, Manoharan R, Jayaraj RL, Elangovan N. Alzheimer's disease: A molecular view of β-amyloid induced neurodegeneration, mechanisms and prevention. Int J Neurosci. 2019;129(4):333–50.

12. Forner S, Baglietto-Vargas D, Martini AC, Trujillo-Estrada L, LaFerla FM. Synaptic impairment in Alzheimer's disease: a dysregulated symphony. Trends Neurosci. 2017;40(6):347–57.
13. Agrawal M, Biswas A. Molecular diagnostics of neurodegenerative disorders. Front Mol Biosci. 2015;2:54.
14. Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Green RC, et al. The Alzheimer's Disease Neuroimaging Initiative: a review of papers published since its inception. Alzheimers Dement. 2012;8(1 Suppl):S1–68.
15. Dugger BN, Dickson DW. Pathology of neurodegenerative diseases. Cold Spring Harb Perspect Biol. 2017;9(7):a028035.
16. Rajmohan R, Reddy PH. Amyloid-beta and phosphorylated tau accumulations cause abnormalities at synapses of Alzheimer's disease neurons. J Alzheimers Dis. 2017;57(4):975–99.
17. Jellinger KA. Neuropathological aspects of Alzheimer disease, Parkinson disease and frontotemporal dementia. Neurodegener Dis. 2008;5(3–4):118–21.
18. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med. 2011;1(1):a006189.
19. Oakley H, Cole SL, Logan S, Maus E, Shao P, Craft J, et al. Intraneuronal β-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation. J Neurosci. 2006;26(40):10129–40.
20. Iqbal K, Liu F, Gong CX, Grundke-Iqbal I. Tau in Alzheimer disease and related tauopathies. Curr Alzheimer Res. 2010;7(8):656–64.
21. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med. 2011;1(1):a006189.
22. Brier MR, Gordon B, Friedrichsen K, McCarthy J, Stern A, Christensen J, et al. Tau and Aβ imaging, CSF measures, and cognition in Alzheimer's disease. Sci Transl Med. 2016;8(338):338ra66.
23. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med. 2016;8(6):595–608.
24. Uddin MS, Kabir MT, Rahman MS, Behl T, Jeandet P, Ashraf GM, et al. Revisiting the amyloid cascade hypothesis: From anti-Aβ therapeutics to auspicious new ways for Alzheimer's disease. Int J Mol Sci. 2020;21(16):5858.
25. D'Argenio V, Sarnataro D. New insights into the molecular bases of familial Alzheimer's disease. J Pers Med. 2020;10(1):26.
26. Alavi Naini SM, Soussi-Yanicostas N. Tau hyperphosphorylation and oxidative stress, a critical vicious circle in neurodegenerative tauopathies? Oxid Med Cell Longev. 2015;2015:151979.
27. Liu B, Liu J, Shi JS. SIRT1 and Alzheimer's disease: modulation of amyloid-beta peptide generation. Neurosci Bull. 2008;24(5):439–44.
28. Lesné S, Koh MT, Kotilinek L, Kayed R, Glabe CG, Yang A, et al. A specific amyloid-beta protein assembly in the brain impairs memory. Nature. 2006;440(7082):352–7.
29. Liao D, Miller EC, Teravskis PJ. Tau acts as a mediator for Alzheimer's disease-related synaptic deficits. Eur J Neurosci. 2014;39(7):1202–13.
30. Bloom GS. Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis. JAMA Neurol. 2014;71(4):505–8.
31. Evans DA, Funkenstein HH, Albert MS, Scherr PA, Cook NR, Chown MJ, et al. Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. JAMA. 1989;262(18):2551–6.
32. Green RC, Cupples LA, Go R, Benke KS, Edeki T, Griffith PA, et al. Risk of dementia among white and African American relatives of patients with Alzheimer disease. JAMA. 2002;287(3):329–36.
33. Harris JR, editor. New insights into Alzheimer's disease. Vol. 2. Amsterdam: Elsevier; 2006.
34. Scheuner D, Eckman C, Jensen M, Song X, Citron M, Suzuki N, et al. Secreted amyloid beta-protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease. Nat Med. 1996;2(8):864–70.
35. Duyckaerts C, Potier MC, Delatour B. Alzheimer disease models and human neuropathology: similarities and differences. Acta Neuropathol. 2008;115(1):5–38.
36. Mayeux R, Stern Y. Epidemiology of Alzheimer disease. Cold Spring Harb Perspect Med. 2012;2(8):a006239.
37. Viña J, Lloret A, Giraldo E, Badía MC, Alonso MD. Antioxidant pathways in Alzheimer's disease: possibilities of intervention. Curr Pharm Des. 2011;17(35):3861–4.

38. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;297(5580):353–6.
39. Dhillon S. Aducanumab: First approval. Drugs. 2021;81(12):1437–42.
40. Tolar M, Abushakra S, Hey JA, Porsteinsson A, Sabbagh M. Aducanumab, gantenerumab, BAN2401, and ALZ-801—the first wave of amyloid-targeting drugs for Alzheimer's disease with potential for near term approval. Alzheimers Res Ther. 2020;12(1):95.
41. Budd Haeberlein S, Aisen PS, Barkhof F, Chalkias S, Chen T, Cohen S, et al. Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. J Prev Alzheimers Dis. 2022;9(2):197–210.
42. Haeberlein SB, von Hehn C, Tian Y, Chalkias S, Muralidharan KK, Chen T, et al. Emerge and Engage topline results: Two phase 3 studies to evaluate aducanumab in patients with early Alzheimer's disease. Alzheimers Dement. 2019;15(Suppl 7):P2734–5.
43. Lin YT, Seo J, Gao F, Feldman HM, Wen HL, Penney J, et al. APOE4 causes widespread molecular and cellular alterations associated with Alzheimer's disease phenotypes in human iPSC-derived brain cell types. Neuron. 2018;98(6):1141–54.e7.
44. Karran E, De Strooper B. The amyloid cascade hypothesis: are we poised for success or failure? J Neurochem. 2016;139(Suppl 2):237–52.
45. Congdon EE, Sigurdsson EM. Tau-targeting therapies for Alzheimer disease. Nat Rev Neurol. 2018;14(7):399–415.
46. Long JM, Holtzman DM. Alzheimer disease: an update on pathobiology and treatment strategies. Cell. 2019;179(2):312–39.
47. Knopman DS, Amieva H, Petersen RC, Chételat G, Holtzman DM, Hyman BT, et al. Alzheimer disease. Nat Rev Dis Primers. 2021;7(1):33.
48. Peng C, Trojanowski JQ, Lee VM. Protein transmission in neurodegenerative disease. Nat Rev Neurol. 2020;16(4):199–212.
49. Nisbet RM, Polanco JC, Ittner LM, Götz J. Tau aggregation and its interplay with amyloid-β. Acta Neuropathol. 2015;129(2):207–20.
50. Robinson JL, Lee EB, Xie SX, Rennert L, Suh E, Bredenberg C, et al. Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. Brain. 2018;141(7):2181–93.
51. Pascoal TA, Benedet AL, Ashton NJ, Kang MS, Therriault J, Chamoun M, et al. Microglial activation and tau propagate jointly across Braak stages. Nat Med. 2021;27(9):1592–9.
52. Henstridge CM, Hyman BT, Spires-Jones TL. Beyond the neuron–cellular interactions early in Alzheimer disease pathogenesis. Nat Rev Neurosci. 2019;20(2):94–108.
53. Hampel H, Vassar R, De Strooper B, Hardy J, Willem M, Singh N, et al. The β-secretase BACE1 in Alzheimer's disease. Biol Psychiatry. 2021;89(8):745–56.
54. Wang Y, Cella M, Mallinson K, Ulrich JD, Young KL, Robinette ML, et al. TREM2 lipid sensing sustains the microglial response in an Alzheimer's disease model. Cell. 2015;160(6):1061–71.
55. Ulland TK, Song WM, Huang SC, Ulrich JD, Sergushichev A, Beatty WL, et al. TREM2 maintains microglial metabolic fitness in Alzheimer's disease. Cell. 2017;170(4):649–63.e13.
56. Ghosh AK, Osswald HL. BACE1 (β-secretase) inhibitors for the treatment of Alzheimer's disease. Chem Soc Rev. 2014;43(19):6765–813.
57. Egan MF, Kost J, Tariot PN, Aisen PS, Cummings JL, Vellas B, et al. Randomized trial of verubecestat for prodromal Alzheimer's disease. N Engl J Med. 9 2019;380(15):1408–20.
58. Makin S. The amyloid hypothesis on trial. Nature. 2018;559(7715):S4–7.
59. Mullard A. Alzheimer amyloid hypothesis lives on. Nat Rev Drug Discov. 2021;20(1):3–6.
60. Honig LS, Vellas B, Woodward M, Boada M, Bullock R, Borrie M, et al. Trial of solanezumab for mild dementia due to Alzheimer's disease. N Engl J Med. 2018;378(4):321–30.
61. Selkoe DJ. Alzheimer disease and aducanumab: adjusting our approach. Nat Rev Neurol. 2019;15(7):365–6.
62. Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature. 2016;537(7618):50–6.
63. Ostrowitzki S, Lasser RA, Dorflinger E, Scheltens P, Barkhof F, Nikolcheva T, et al. A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. Alzheimers Res Ther. 2017;9(1):95.
64. Panza F, Lozupone M, Logroscino G, Imbimbo BP. A critical appraisal of amyloid-β-targeting therapies for Alzheimer disease. Nat Rev Neurol. 2019;15(2):73–88.

65. Ostrowitzki S, Deptula D, Thurfjell L, Barkhof F, Bohrmann B, Brooks DJ, et al. Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab. Arch Neurol. 2012;69(2):198–207.
66. Tucker S, Möller C, Tegerstedt K, Lord A, Laudon H, Sjödahl J, et al. The murine version of BAN2401 (mAb158) selectively reduces amyloid-β protofibrils in brain and cerebrospinal fluid of tg-ArcSwe mice. J Alzheimers Dis. 2015;43(2):575–88.
67. Swanson CJ, Zhang Y, Dhadda S, Wang J, Kaplow J, Lai RYK, et al. Trial of BAN2401 for early Alzheimer's disease. N Engl J Med. 2021;385(18):1649–61.
68. Van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in early Alzheimer's disease. N Engl J Med. 2023;388(1):9–21.
69. Høilund-Carlsen PF, Frokjaer JB, Rubin P, Alavi A. Lecanemab: the need for new trials. J Alzheimers Dis. 2023;94(1):1–5.
70. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al. Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA. 2023;330(6):512–27.
71. Mintun MA, Lo AC, Duggan Evans C, Wessels AM, Ardayfio PA, Andersen SW, et al. Donanemab in early Alzheimer's disease. N Engl J Med. 2021;384(18):1691–704.
72. Tolar M, Abushakra S, Hey JA, Porsteinsson A, Sabbagh M. Aducanumab, gantenerumab, BAN2401, and ALZ-801—the first wave of amyloid-targeting drugs for Alzheimer's disease with potential for near term approval. Alzheimers Res Ther. 2020;12(1):95.
73. Høilund-Carlsen PF, Edenbrandt L, Alavi A. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(1):88–106.
74. Tarawneh R, Holtzman DM. The clinical problem of symptomatic Alzheimer disease and mild cognitive impairment. Cold Spring Harb Perspect Med. 2012;2(5):a006148.
75. Rabinovici GD. Controversy and progress in Alzheimer's disease—FDA approval of aducanumab. N Engl J Med. 2021;385(9):771–4.
76. Knopman DS, Perlmutter JS. Prescribing Aduhelm in the United States—CMS proposes an answer. Nat Rev Neurol. 2022;18(3):125–6.
77. Alexander GC, Emerson S, Kesselheim AS. Evaluation of aducanumab for Alzheimer disease: scientific evidence and regulatory review involving efficacy, safety, and futility. JAMA. 2021;325(17):1717–8.
78. Høilund-Carlsen PF, Frokjaer JB, Edenbrandt L, Alavi A. The FDA approval of aducanumab for Alzheimer's disease: The need for a paradigm shift. J Alzheimers Dis. 2022;85(2):427–30.
79. Whitehouse PJ. The end of Alzheimer's disease—not with a bang but a whimper. J Alzheimers Dis. 2014;40(3):S141–3.
80. Panza F, Seripa D, Solfrizzi V, Imbimbo BP, Lozupone M, Santamato A, et al. Targeting amyloid-β peptide in Alzheimer's disease: biological and pharmacological perspectives. Expert Opin Ther Targets. 2016;20(7):693–702.
81. Cummings J, Aisen PS, DuBois B, Frölich L, Jack CR, Jones RW, et al. Drug development in Alzheimer's disease: the path to 2025. Alzheimers Res Ther. 2016;8(1):39.
82. Yiannopoulou KG, Papageorgiou SG. Current and future treatments for Alzheimer's disease. Ther Adv Neurol Disord. 2013;6(1):19–33.
83. Reiss AB, Arain HA, Stecker MM, Siegart NM, Kasselman LJ. Amyloid toxicity in Alzheimer's disease. Rev Neurosci. 2018;29(6):613–27.
84. Novak P, Schmidt R, Kontsekova E, Zilka N, Kovacech B, Skrabana R, et al. Safety and immunogenicity of the tau vaccine AADvac1 in patients with Alzheimer's disease: a randomised, double-blind, placebo-controlled, phase 1 trial. Lancet Neurol. 2017;16(2):123–34.
85. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimers Res Ther. 2014;6(4):37.
86. Schindler SE, Bollinger JG, Ovod V, Mawuenyega KG, Li Y, Gordon BA, et al. High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis. Neurology. 2019;93(17):e1647–59. doi: 10.1212/WNL.0000000000008081.
87. Janelidze S, Mattsson N, Palmqvist S, Smith R, Beach TG, Serrano GE, et al. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. Nat Med. 2020;26(3):379–86. doi: 10.1038/s41591-020-0755-1.

88. Palmqvist S, Tideman P, Cullen N, Zetterberg H, Blennow K, Dage JL, et al. Prediction of future Alzheimer's disease dementia using plasma phospho-tau combined with other accessible measures. Nat Med. 2021;27(6):1034–42. doi: 10.1038/s41591-021-01348-z.
89. De Simone MS, De Tollis M, Fadda L, Perri R, Caltagirone C, Carlesimo GA. Lost or unavailable? Exploring mechanisms that affect retrograde memory in mild cognitive impairment and Alzheimer's disease patients. J Neurol. 2020;267(1):113–24. doi: 10.1007/s00415-019-09559-8.
90. De Simone MS, Perri R, Fadda L, De Tollis M, Turchetta CS, Caltagirone C, et al. Different deficit patterns on word lists and short stories predict conversion to Alzheimer's disease in patients with amnestic mild cognitive impairment. J Neurol. 2017;264(11):2258–67. doi: 10.1007/s00415-017-8623-8.
91. De Simone MS, Perri R, Fadda L, Caltagirone C, Carlesimo GA. Predicting progression to Alzheimer's disease in subjects with amnestic mild cognitive impairment using performance on recall and recognition tests. J Neurol. 2019;266(1):102–11. doi: 10.1007/s00415-018-9108-0.
92. Di Lorenzo F, Motta C, Casula EP, Bonnì S, Assogna M, Caltagirone C, et al. LTP-like cortical plasticity predicts conversion to dementia in patients with memory impairment. Brain Stimul. 2020;13(5):1175–82. doi: 10.1016/j.brs.2020.05.013.
93. Giorgio J, Landau SM, Jagust WJ, Tino P, Kourtzi Z, Alzheimer's Disease Neuroimaging Initiative. Modelling prognostic trajectories of cognitive decline due to Alzheimer's disease. Neuroimage Clin. 2020;26:102199. doi: 10.1016/j.nicl.2020.102199.
94. Thung K-H, Yap P-T, Adeli E, Lee S-W, Shen D. Conversion and time-to-conversion predictions of mild cognitive impairment using low-rank affinity pursuit denoising and matrix completion. Med Image Anal. 2018;45:68–82. doi: 10.1016/j.media.2018.01.002.
95. Cox DR. Regression models and life-tables. Breakthroughs Stat. 1992;372:527–41.
96. Cox DR, Oakes D. Analysis of survival data. Boca Raton, FL: CRC Press; 1984.
97. Liu K, Chen K, Yao L, Guo X. Prediction of mild cognitive impairment conversion using a combination of independent component analysis and the Cox model. Front Hum Neurosci. 2017;11:33. doi: 10.3389/fnhum.2017.00033.
98. Li S, Okonkwo O, Albert M, Wang M-C. Variation in variables that predict progression from MCI to AD dementia over duration of follow-up. Am J Alzheimers Dis. 2013;2:12–28. doi: 10.7726/ajad.2013.1002.
99. Franzmeier N, Koutsouleris N, Benzinger T, Goate A, Karch CM, Fagan AM, et al. Predicting sporadic Alzheimer's disease progression via inherited Alzheimer's disease-informed machine-learning. Alzheimers Dement. 2020;16(3):501–11. doi: 10.1002/alz.12032.
100. Koch G, Belli L, Giudice TL, Lorenzo FD, Sancesario GM, Sorge R, et al. Frailty among Alzheimer's disease patients. CNS Neurol Disord Drug Targets. 2013;12(4):507–11. doi: 10.2174/18715273113120400010.
101. Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. JAMA. 2014;312(23):2551–61. doi: 10.1001/jama.2014.13806.
102. Rosenberg PB, Lyketsos C. Mild cognitive impairment: searching for the prodrome of Alzheimer's disease. World Psychiatry. 2008;7(2):72–8. doi: 10.1002/j.2051-5545.2008.tb00159.x.
103. Gamberger D, Lavrač N, Srivatsa S, Tanzi RE, Doraiswamy PM. Identification of clusters of rapid and slow decliners among subjects at risk for Alzheimer's disease. Sci Rep. 2017;7:6763. doi: 10.1038/s41598-017-06624-y.
104. Gamberger D, Ženko B, Mitelpunkt A, Lavrač N. Homogeneous clusters of Alzheimer's disease patient population. Biomed Eng Online. 2016;15(Suppl 1):78. doi: 10.1186/s12938-016-0183-0.