Applications of machine learning and multimodal integration for the early diagnosis of neurodegenerative diseases (Review)

SARANYA VELMURUGAN[1], SHIEK WAHEEDA[2], LANGESWARAN KULANTHAIVEL[3] and GOWTHAM KUMAR SUBBARAJ[1]

[1]Faculty of Allied Health Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Chennai, Tamil Nadu 603103, India; [2]Department of Physiology, Kirupananda Variyar Medical College and Hospital, Vinayaka Mission Research Foundation (Deemed to be University), Salem, Tamil Nadu 636308, India; [3]Department of Biomedical Sciences, Alagappa University, Karaikudi, Tamil Nadu 630001, India

Received June 11, 2025; Accepted September 24, 2025

DOI: 10.3892/wasj.2025.403

Abstract. Neurodegenerative disorders (NDDs) such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis are critical worldwide health issues. Recent diagnostic methods primarily rely on biomarkers and clinical evaluations, often exhibiting insufficient specificity and sensitivity during the initial stages of illness. The present review discusses the machine learning (ML) techniques used to enhance the early prediction and detection of NDDs. The use of ML in analyzing many data modalities, including genetic biomarkers, molecular and cellular biomarkers, neuroimaging data, and cognitive/behavioral evaluations is also discussed. Research with ML techniques, including convolutional neural networks, support vector machines and recurrent neural networks has demonstrated substantial improvements in diagnostic precision for numerous NDDs, often exceeding conventional methodologies. Moreover, multimodal integration techniques that integrate various types of data further enhance prediction power. However, despite the positive results, challenges such as data standardization, privacy concerns and the requirement for robust validation across numerous populations persist. Addressing these challenges will be crucial for translating the potential of ML into clinically impactful tools for the early diagnosis, personalized treatment and improved management of NDDs.

Correspondence to: Dr Gowtham Kumar Subbaraj, Faculty of Allied Health Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Rajive Gandhi Salai, Kelambakkam, Chengalpattu, Kanchipuram, Chennai, Tamil Nadu 603103, India
E-mail: gowtham_phd@yahoo.com

Abbreviations: NDDs, neurodegenerative disorders; AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; ML, machine learning; CNNs, conventional neural networks; SVMs, support vector machines; WHO, World Health Organization; SNP, single nucleotide polymorphism; AI, artificial intelligence; DL, deep learning; PET, positron emission tomography; MRI, magnetic resonance imaging; MCI, mild cognitive impairment

Key words: biomarker discovery, machine learning, early diagnosis, multimodal imaging, neurodegenerative disease

Contents

1. Introduction

Neurodegenerative diseases (NDDs) are the second leading cause of mortality worldwide, constituting an increasing public health concern (1). Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common NDDs, affecting 35 million and 6 million individuals worldwide, respectively (2). Dementia currently affects ~50 million individuals, with projections suggesting an increase to 130 million by the year 2050. AD is the predominant NDD, including 60-70% of all cases of dementia (3). According to the Alzheimer's Association, an estimated 6.7 million Americans aged ≥65 years are currently living with Alzheimer's dementia, a number projected to nearly double to 13.8 million by 2060 in the absence of disease-modifying treatments. AD is the sixth-leading cause of mortality in the USA overall, and the fifth-leading cause among those aged ≥65 years. In 2019, 121,499 deaths were attributed to AD, and between 2000 and 2019, deaths from

AD increased by >145%, in contrast to declines in stroke, heart disease and HIV-related mortality (4). The World Health Organization (WHO) reports that the prevalence of PD has multiplied over the past 25 years, affecting >8.5 million individuals worldwide. In 2019, PD was responsible for 329,000 deaths, more than double the number of deaths that occurred in 2000, and resulted in 5.8 million disability-adjusted life years, which represents an 81% increase since the year 2000 (5). Motor neuron disease, commonly known as amyotrophic lateral sclerosis (ALS), affects individuals globally, with an incidence rate of ~2 per 100,000 person-years, a prevalence of 6 to 9 per 100,000 person-years, and a lifetime risk estimated at 1 in 350 (6). As the population increases and society ages, a greater number of individuals are attaining ages associated with a high prevalence of neurological illnesses. The etiology of NDD is multifaceted and intricate. Progress in genomic technology has revealed mutations linked to disease (7). However, in the case of NDDs, such as AD, PD and ALS, a considerable number of sporadic and even familial cases have uncleared genetic origins. Furthermore, not all identified mutations are fully penetrant or result in disease. Instead, a combination of genetic risk factors may affect the vulnerability of an individual to developing NDDs (8). Single-nucleotide polymorphism (SNP)-based heritability estimates range from ~16 to36% for PD, 8 to 61% for ALS, and 38 to 66% for AD. These estimations nonetheless indicate that non-genetic variables have a significant effect (9). As a result, it is generally acknowledged that environmental exposures, also known as the exposome, play a major role in the onset and course of NDD (10).

Generally, NDDs are gradual, irreversible and linked to functional loss. NDDs manifest physiologically as demyelination, dendritic loss and neuronal death (11). A slow and cumulative loss of cognitive abilities (dementia) and movement abilities (ataxia) results from the degeneration of neural structures, which may lead to mental impairment, functional loss and debilitation. Despite being more common among the elderly, NDDs may affect individuals of any age (12). The early identification of NDDs is crucial for facilitating rapid therapies and controlling these progressive disorders efficiently. There is increasing interest in identifying early diagnostic tools and novel treatment strategies for NDDs (13). Traditional biomarkers, including protein biomarkers, exosomes and microRNAs (miRNAs), exhibit promise in detecting neural dysfunction prior to the appearance of clinical symptoms (14-16). Researchers investigate these biomarkers, combined with other laboratory and biochemical indicators, for their potential in early diagnosis and evaluation of disease development (17).

The requirement for biological material and inpatient treatment limits the use of analog biomarkers for identifying NDDs (18). Although these challenges exist, the progress in bioassays and the identification of biological indicators in blood, urine, tissue, plasma and serum indicates the potential for overcoming these limitations. However, the complete verification of the therapeutic efficacy of these biomarkers remains elusive (19). Further research is warranted to standardize these findings and to evaluate their effectiveness in identifying the early stages of the illness. A search for an optimal biomarker for NDDs continues to guarantee a reliable and accurate diagnosis in the earliest clinical phases. Conversely, digital technologies that provide objective, high-frequency data are being investigated to solve the existing subjective assessments of NDDs (20).

In recent years, artificial intelligence (AI) has emerged as a transformative tool in health care (21). Machine learning (ML), a subset of AI, has been increasingly favored over other deep learning or traditional statistical methods due to its ability to learn complex patterns from high-dimensional data without extensive feature engineering. ML has demonstrated significant potential in enhancing the early diagnosis, disease monitoring and predictive models of NDDs (22). ML algorithms can analyze complex, high-dimensional biological datasets to identify patterns associated with disease onset and progression. By integrating neuroimaging, genetic, molecular, and behavioral data, ML models also improve diagnostic accuracy and facilitate personalized treatment approaches (23). Additionally, wearable sensors and remote monitoring systems leverage ML to track disease symptoms in real-time, provoiding a non-invasive and scalable approach to early diagnosis (24).

The present review discusses the use of ML in the early diagnosis of NDDs, emphasizing key areas, such as biomarker discovery, genetic analysis, neuroimaging and cognitive assessment. It also explains the advantages of ML over traditional methods in capturing complex associations and improving predictive accuracy. The essential ML techniques, feature selection strategies and data preprocessing methods relevant to biomedical fields are emphasized. Additionally, the improved diagnostic accuracy and the ability to address challenges related to data consistency and privacy using combined multimodal data sources are discussed. By reviewing the latest advances in ML-based NDD research, the present review aimed to provide insight into the role of AI in the early detection and management of NDDs.

2. Pathophysiology of neurodegenerative diseases: Overview

AD is marked by a slow and advancing neurodegeneration due to the death of neuronal cells, significantly affecting cognitive abilities. This neurodegenerative process usually begins in the entorhinal cortex of the hippocampus, an area vital for memory processing (25). The formation of neurofibrillary tangles is composed of phosphorylated tau protein, strongly associated with cognitive impairment, compared to the amyloid plaques. Neurofibrillary tangles and amyloid plaques are essential for the neuropathological diagnosis of AD (11). Neurofibrillary tangles first develop in the entorhinal cortex and hippocampus before moving to the isocortex, which is how AD proceeds stereotypically. This progression is divided into phases that correspond to the clinical presentation of dementia and indicate the growing severity of the disease (26).

The degeneration of dopaminergic neurons in the substantia nigra is the main characteristic of PD, a complex neurodegenerative illness that causes motor symptoms, such as bradykinesia, stiffness and tremors (27). The first known gene linked to PD is the synuclein alpha (SNCA) gene, which codes for α-synuclein. PD with autosomal-dominant inheritance patterns showed that an early onset may be due to mutations in SNCA (28). The α-synuclein protein, a key component of

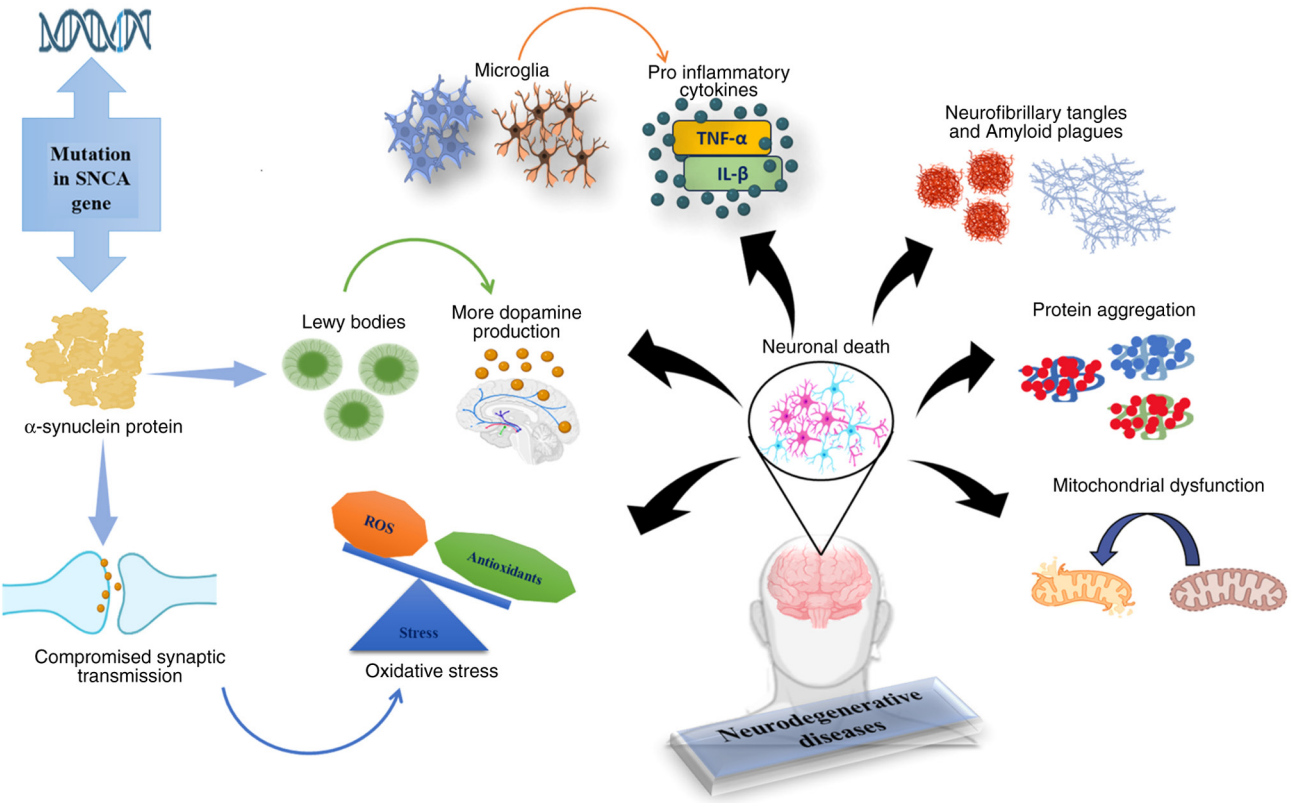

Figure 1. General pathophysiological factors of neurodegenerative diseases. SNCA, synuclein alpha.

Lewy bodies in the brains of patients with PD, destroys dopaminergic neurons. More dopamine may worsen dopaminergic neuron degeneration. While α-synuclein is advantageous for dopaminergic neurons, its overexpression may destroy them when paired with dopamine (29). SNCA aggregation interferes with cellular function, resulting in compromised synaptic transmission and increased oxidative stress, which exacerbates neuronal cell death (30). Mutations in genes, such as SNCA, leucine-rich repeat kinase 2, PTEN-induced putative kinase 1, Parkin RBR E3 ubiquitin protein ligase, protein deglycase and glucosylceramidase beta 1 cause ~10-15% of cases of familial PD (31). Neuroinflammation significantly contributes to the progression of PD, with microglial activation noted in post-mortem studies of affected individuals. This dysfunctional immune response can worsen neuronal stress and death, as microglia may release pro-inflammatory cytokines that aid in neurodegeneration. Increased levels of inflammatory markers, such as IL-1β and TNF-α have been linked to the severity and progression of the disease (Fig. 1) (32).

Several pathways that interfere with the pathogenesis of ALS, such as mitochondrial dysfunction, neuroinflammation, oxidative stress, axonal damage, protein aggregation and excitotoxicity, have been suggested to play a role (33). TAR DNA-binding protein 43 (TDP-43) is the primary component of inclusions observed in >95% of patients with ALS. This RNA- and DNA-binding protein is critical for key processes, including transcription, splicing and RNA transport (34). TDP-43 mostly exists in the nucleus; however, in ALS, it may be mislocalized to the cytoplasm, resulting in nuclear depletion and protein aggregation (35). Protein clumps impair cellular protein homeostasis, eliciting stress. Molecular chaperones facilitate the refolding of misfolded proteins, whereas excess aggregates are eliminated by the ubiquitin-proteasome system or lysosomal autophagy (36). The buildup of misfolded superoxide dismutase 1 (mSOD1) in the mitochondria adversely affects spinal motor neurons and skeletal muscles, resulting in the release of aberrant ATP, elevated reactive oxygen species production and apoptosis (37). A dominant missense mutation in the SOD1 gene, which is a major cause of ALS, results in the creation of insoluble, ubiquitin-positive inclusion bodies in motor neurons. While chaperones play a role in protein folding, SOD1 aggregates capture heat shock proteins, leading to endoplasmic reticulum stress and the accumulation of toxic substances (38). Autophagy mitigates mutant SOD1 toxicity, yet it often proves inadequate, resulting in the accumulation of aggregates and higher cell mortality rates (39). Genetic mutations are key factors in the pathophysiology of ALS. Of note, >20 genes have been shown to be associated with ALS, with the most prevalent mutations identified in the C9 or f72, TDP-43, ubiquitin-2, VCP, TANK-binding kinase 1, SOD1, TARDBP and FUS genes (40).

3. Diagnostic challenges and limitations of neurodegenerative disease

The diagnosis of NDDs is difficult since symptoms often develop gradually. Numerous NDDs have overlapping symptoms, potentially resulting in misdiagnosis (41). Furthermore, the dependence on clinical criteria implies that a number of pathological alterations may remain undetected until significant brain damage has occurred. This delay in diagnosis may lead to lost possibilities for early intervention (42).

Discrimination and misinformation about cognitive decline could prevent individuals from seeking therapy, delaying early identification (43). Current diagnostic methods depend on clinical assessments and standard neuropsychological testing, which may be inadequate for detecting early underlying pathologies in NDDs. Blood biomarkers, such as neurofilament light chain, phosphorylated tau, amyloid-β and total tau, have been proposed to assist in diagnosis (44). A notable issue is the fluctuation in biomarker levels, which are affected by variables, such as age, sex and comorbidities, potentially confusing interpretations. While several biomarkers have impressive sensitivity, their specificity for NDDs is often inadequate, resulting in possible false positives (45). Cerebrospinal fluid (CSF) biomarkers serve as direct indicators of the central nervous system, offering insights into pathological processes (46). Lumbar puncture for CSF collection is invasive and may be poorly tolerated. Not all healthcare environments provide it, and it may be costly. The conditions of sample processing and analysis may also influence diagnostic accuracy (47). Imaging biomarkers, such as diffusion imaging, magnetic resonance imaging (MRI) and positron emission tomography (PET), allow for the visualization of brain changes. These approaches detect neurodegenerative processes before symptoms appear. Magnetic resonance elastography examines tissue properties to enhance early diagnosis (48). Advanced imaging techniques, such as PET scans, may be costly and less accessible. Certain procedures expose patients to radiation, raising safety concerns. Furthermore, outcomes may differ based on patient attributes and circumstances, resulting in possible misinterpretations (49). Genetic biomarkers, such as mutations, SNPs and miRNAs, provide insight into disease causes and susceptibility. Identifying effective biomarkers for NDDs is challenging due to the intricate connections between hereditary and environmental variables (50). Furthermore, genetic markers may vary across populations, affecting their effectiveness and therapeutic significance. Initial genetic testing prompts ethical issues, including privacy, potential discrimination, and the psychological impact on those at risk (51).

4. Fundamentals of machine learning models and techniques

Recent research highlights the potential of emerging technologies to enhance diagnostics. There is growing interest in the use of ML to analyze diagnostic data effectively (52). ML will be crucial in developing learning healthcare systems that integrate various data sources with complex algorithms. This will provide continuous, data-informed insight to enhance biomedical research, public health and the quality of healthcare (53). The majority of ML methods can be grouped into three categories, with supervised ML being the first. This method trains a model on input characteristics with known results. In medicine, it may link height, weight and smoking status to the 5-year diabetes risk. After training, the system will predict fresh data outcomes with discrete or continuous scores (54). Unlike supervised learning, unsupervised learning operates without a predetermined outcome. This strategy involves algorithms independently detecting patterns without human involvement. Consequently, unsupervised algorithms are investigative and intended to reveal hidden patterns or clusters within datasets (55). Reinforcement learning entails a system engaging with its environment, promoting favorable actions and discouraging unfavorable actions. These approaches are used in a number of medical operations, including disease diagnosis (56). Deep learning (DL), a branch of ML, is characterized by the use of several layers, each signifying different levels of abstraction. In this framework, each layer evaluates the information obtained from the previous layer and transmits the results to the subsequent layer (57).

Selection of features, data preprocessing and assessment of matrices for biomedical applications. Feature selection is a common method in ML to reduce dimensionality by identifying a subset of relevant features based on established criteria (58). Reducing noise and removing non-informative features are essential to tackle the 'curse of dimensionality', which arises when the number of features exceeds the number of observations (59). Feature selection allows for the identification of high-risk genes associated with cancer. As microarray gene expression data are high-dimensional, it is essential to perform critical feature extraction techniques, including the t-test, Wilcoxon sign rank sum test test, random forest, Boruta and LASSO, among others (60). Feature selection techniques may be classified as filters, embedding methods and wrappers according to their association with the learning algorithm (61). Data preprocessing entails the preparation of raw data to render it appropriate for ML analysis. This phase is essential in biological applications where data may often be noisy or partial. Data preparation techniques include normalization, management of missing values and outlier identification (62). Data preprocessing includes data cleansing and feature engineering. Data cleaning removes duplicate, incorrect, irrelevant and missing data. This requires a detailed knowledge of the data, its collection context, and the application of the model in the environment. Clinicians and data scientists from different fields need to collaborate to clean data (63). Feature engineering employs a range of statistical methods to transform data into a format that ML algorithms can use more effectively. Typical procedures in feature engineering comprise transformation, dimensionality reduction, data type conversion, data normalization and feature selection, all aimed at fulfilling the requirements of ML algorithms (64). ML performance measures are essential for assessing diagnostic models in healthcare. Standard metrics include classification and regression measures, which need to be analyzed in light of class imbalance, prevalence and cost-benefit trade-offs (65). Effective validation methods, including cross-validation and distinct test sets, are crucial to prevent data leakage and provide impartial estimates. In binary classification tasks, measurements such as sensitivity, specificity, and the area under the ROC curve are often used (Fig. 2) (66). Researchers and clinicians must comprehend these parameters to evaluate ML studies objectively and determine how they could affect patient treatment (67). When assessing ML models, it is crucial to consider the sample size as well as the issues of overfitting and underfitting. Researchers have created tools to compute and visualize many performance indicators, thereby aiding in the comparison and understanding of ML models (68).

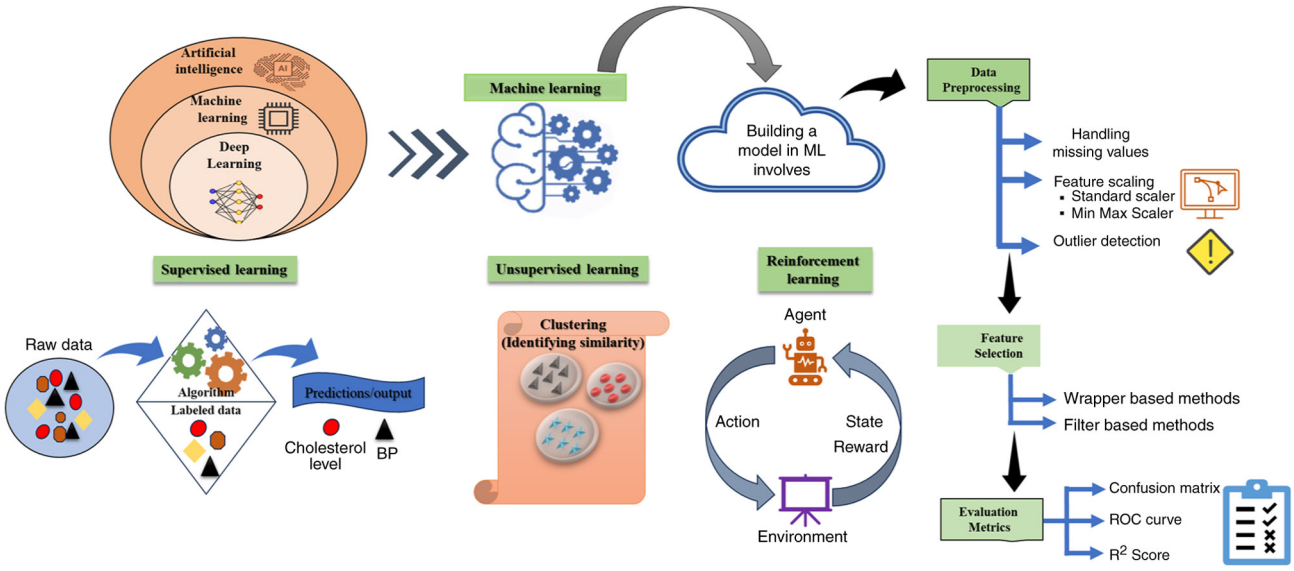

Figure 2. Overview of artificial intelligence and machine learning techniques. ML, machine learning.

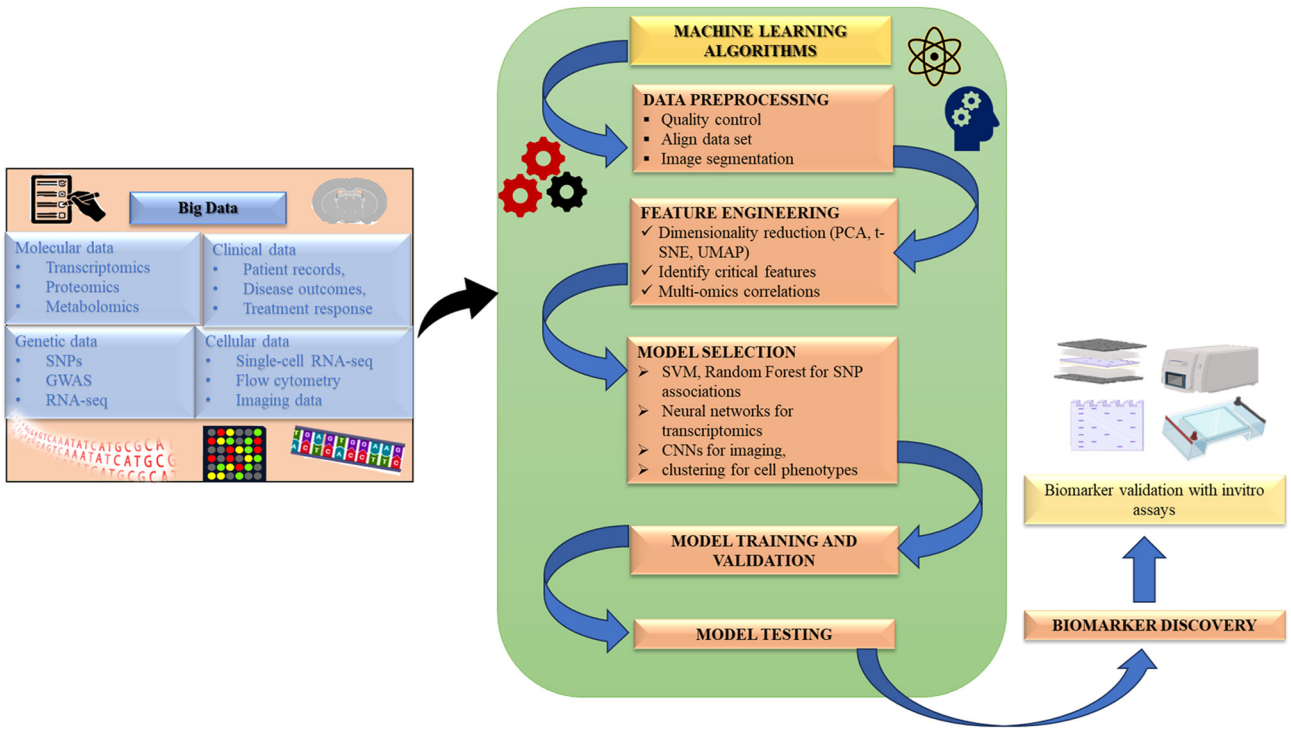

Figure 3. Identification of genetic, molecular, and cellular biomarkers using machine learning models. SNPs, single nucleotide polymorphisms; GWAS, genome-wide association studies; SVM, support vector machine; CNNs, conventional neural networks.

5. Machine learning in biomarker discovery and analysis

ML is an effective tool for the diagnosis of various diseases and analyzing data. ML approaches, such as DL and support vector machines (SVMs), examine intricate data from genomics, proteomics and imaging to identify molecular signatures and biomarkers (Fig. 3) (69). These approaches provide advantages over traditional statistical techniques in handling large, high-dimensional datasets. However, challenges such as data privacy and overfitting persist. Explainable ML models could mitigate these issues by providing mechanistic insights into predictions, thus improving the robustness and reliability of biomarker discovery.

ML used in genetic biomarkers. Recent research has investigated the use of ML to detect genetic biomarkers for the diagnosis of NDDs. Broadly, these studies fall into three categories, such as: i) Large-scale genomic/transcriptomic analyses; ii) miRNA and blood transcript investigations; and iii) DNA methylation or SNP-based approaches.

In a large-scale genomic study, Lam *et al* analyzed clinical and genetic data from the UK Biobank to create models

that predict motor neuron disease, AD, PD and myasthenia gravis, achieving 88.3% accuracy. They discovered common genetic risk loci shared across NDDs, although reliance on a single biobank may limit generalizability (70). Similarly, transcriptomic and clinical/laboratory data integrating with ML has been used to detect early comorbidities and cognitive impairment with improved accuracy (71). For miRNA and blood transcript-based biomarkers, Li *et al* (72) applied a feature that differentiates normal and neurodegenerative disease subgroups using computational analysis. Boruta's feature selection removed irrelevant features, although mRMR and MCFS prioritized the remaining ones. The appropriate miRNA biomarker set was established, and the correlation between candidate features and NDDs was confirmed. Other studies using random forest classifiers on blood transcript data have reported high sensitivity and specificity in distinguishing AD, PD and ALS from controls, although small sample sizes raise concerns about model robustness (73). In the area of epigenetic and SNP-based approaches, Ren *et al* (74) applied random forest feature selection and ROC diagnostic analysis of genes exhibiting varied methylation patterns to identify optimal gene biomarkers for AD. Differential methylation was identified in eight genes: STAMBPL1, ANKRD34B, FAM82A1, CDKN1C, NOG, CORO2 B and TXNIP. MYNN was the optimal biomarker for AD (74). Although promising, such findings require replication in independent cohorts. Furthermore, ADNI-1 and WGS datasets have been leveraged to evaluate millions of SNPs, with ML algorithms (SMO, NB, TAN and K2) achieving exceptionally high accuracies (98-99.75%) using 500 SNPs. However, these near-perfect results raise the possibility of overfitting, emphasizing the need for validation on external datasets (75). Deep learning approaches have also demonstrated considerable potential. Convolutional neural network (CNN) models applied to blood-based biomarkers for AD and PD have yielded strong predictive performance, with 81% accuracy and ROC AUC values reaching up to 0.889 and 0.743, respectively (76). Research has demonstrated CNNs applied to microarray data, attaining 95-96% accuracy following dimensionality reduction (PCA and SVD) and data augmentation to mitigate overfitting. While these findings are encouraging, heterogeneity in datasets and limited real-world testing remain as major challenges (77). Overall, ML has proven to be highly effective in identifying diverse genetic and molecular biomarkers for NDDs, providing strong predictive accuracy and the potential to enhance early diagnosis. However, numerous studies are constrained by small sample sizes, reliance on single datasets and risks of overfitting. To enable clinical translation, future research is warranted to emphasize validation across larger, more diverse and independent cohorts. A summary of ML approaches applied to genetic and epigenetic biomarkers in NDDs is depicted in Table I (78-87).

Molecular and cellular biomarkers identified through ML. ML has emerged as a powerful method for detecting cellular and molecular biomarkers across the multiple diseases, particularly in cancer research. By integrating high-throughput omics data, such as transcriptomics, proteomics and genomics, ML methods have achieved sensitivities as high as 95% in identifying diagnostic and prognostic biomarkers (88,89). These approaches are particularly valuable in interpreting complex datasets generated from DNA/RNA sequencing, microarrays, and mass spectrometry, enabling the discovery of biomarkers that were previously difficult to detect (69). This highlights the strength of ML in managing high-dimensional datasets where traditional statistical approaches often fail.

Beyond classification accuracy, ML algorithms are also applied to dynamic modelling of biological processes. For example, they have been used to construct ordinary differential equations (ODE) models of cancer signaling networks to find biomarkers and therapeutic targets. Such ODE modelling and tissue-level simulations may predict the necrosis, growth arrest, cancer metastasis, and immune cell invasion (90). While innovative, these methods require extensive validation AS they rely heavily on assumptions about pathway interactions. Another key application of ML is imaging-based biomarker discovery. Techniques, such as advanced pattern analysis have revealed that imaging patterns can predict the survival of patients with glioblastoma, with each subtype exhibiting unique features. Factors, such as cell density, infiltration, microvascularity and blood-brain barrier impairment can be integrated to create predictive biomarkers that enhance diagnosis and therapy (91). This suggests that multimodal ML frameworks combining imaging with molecular data could improve precision medicine in oncology.

Recent research has also demonstrated that ML may identify new molecular markers in a broad spectrum of disorders. Wang *et al* (92) used ML techniques to examine RNA sequencing and microarray data collected from the GEO database. They discovered essential immune cell types and hub genes associated with unstable atherosclerotic plaques, confirming indicators such as CD68, PAM and IGFBP6 by single-cell RNA sequencing, demonstrating the strength of ML in integrating bulk and single-cell data (92). Similarly, Liang *et al* (93) applied SVM-RFE and LASSO regression on GEO datasets and discovered APOLD1 and EPYC as pivotal diagnostic genes for osteoarthritis. They further linked these genes to immune cell activity through CIBERSORT analysis and validated their findings with reverse transcription-polymerase chain reaction and ROC assays, demonstrating the importance of combining computational prediction with wet-lab validation (93). In pancreatic cancer, ML algorithms have discovered proteins, mRNAs, miRNAs and DNA methylation patterns as potential subtype biomarkers. Integrative profiling will improve treatment tactics by validating drug sensitivity biomarkers using pattern recognition algorithms (94). Likewise, in non-smoking females with stage III non-small cell lung cancer, an analysis of GDS3837 gene expression data using XGBoost achieved a robust AUC score of 0.835, suggesting that these biomarkers may facilitate early diagnosis and tailored treatment (95). The integration of ML with molecular profiling methodologies can guide customized cancer therapies, especially in the field of radiation (96). However, challenges remain, such as small or heterogeneous sample sizes, risk of overfitting, and the lack of standardized performance evaluation across studies, which may limit the reproducibility of biomarker discovery. The ML-based identification of molecular and cellular biomarkers in NDDs is summarized in Table II (97-105).

Table I. Machine learning approaches for identifying genetic and epigenetic biomarkers in NDDs.

First author, year of publication	Biomarker type	Dataset	ML Method	Accuracy	Key findings	(Refs.)
Wang, 2025	Purine metabolism genes (PMGs)	GSE6613, GSE7621	Lasso regression, SVM-RFE	AUC=0.769 with a low error rate of 0.231	The diagnostic capacity of these nine PMGs in distinguishing PD was shown to be significant.	(78)
Huang, 2021	Epigenetic bio-markers (brain CpG methylation sites)	Six AD-related brain datasets (cohorts)	EWASplus (supervised machine learning)	ROC/AUC= 0.831/0.962	Predicted hundreds of novel brain CpGs linked to AD; some loci were tested in the lab; found genes that are rich in kinases and interact with known AD genes; EWAS coverage goes beyond array-based approaches.	(79)
Alamro, 2023	Gene expression biomarkers (hub genes, feature-selected genes, miRNAs, TF JUN)	datasets of brain tissue in the Gene Expression Omnibus (GEO) database (GSE5281, GSE48350, and GSE1297)	Machine learning and deep learning (LASSO, Ridge; hub gene ranking: Degree, MNC, MCC, BC, Closeness, Stress Centrality)	AUC=0.979 (for 5 genes from LASSO and Ridge)	Identified five genes that accurately differentiate Alzheimer's disease from healthy controls; 70% of the hub genes that are turned on are known to be targets for AD; 6 miRNAs and TF JUN are connected to hub genes; Overlapping hub genes limit the search for new AD targets.	(80)
Madar, 2021	Differentially expressed genes (CNPY3, GPR84, HIST1H2AB, HIST1H2AE, IFNAR1, LMO3, MYO18A, N4BP2L1, PML, SLC4A4, ST8SIA4, TLE1)	HG-U133_Plus_2 platform GDS2795 GDS4136	SMO/SVM, Logit Boost, other classifiers	Achieved 85 to 90% accuracy	Identified 13 significant DEGs expressed in brain tissue; co-expression networks validated; J48 emerged as the best classifier for distinguishing AD vs. controls	(81)
Lin, 2022	Blood-based gene biomarkers (29 genes, 31 probes)	ADNI database	Random Forest with feature selection	AUC=0.841 (cross-validation), 0.775 (test set); 97% concordance for high-score patients	Found gene biomarkers that may help predict stable MCI patients; a low-invasive, cost-effective way to screen people; and a possible first-tier diagnostic tool for precision medicine.	(82)
Sharma, 2021	Genetic biomarkers (CORO1C, SLC25A46, RAE1,ANKIB1, CRLF3, PDYN, and non-coding RNAs AK057435, BC037880)	Microarray datasets from four brain regions: Prefrontal cortex, Middle temporal gyrus, Hippocampus, Entorhinal cortex	Ensemble of Random Forest and LASSO (feature selection and classification)	99% average accuracy (5-fold cross-validation)	Identified unique and clinically important genetic indicators for Alzheimer's disease across several brain areas, using uncharacterized non-coding RNAs as possible differentiators.	(83)

Table I. Continued.

First author, year of publication	Biomarker type	Dataset	ML Method	Accuracy	Key findings	(Refs.)
Augustine, 2022	Blood-based gene biomarkers (DEGs from microarray)	Three independent PD microarray datasets (blood samples); independent test: GSE72267	Two-layer embedded wrapper feature selection and classification with 9 ML models, including SVM-R, DNN	AUC=0.821 (SVM-R), 0.82 (DNN) on the independent dataset	Found a strong blood-based gene signature that can be used to detect early signs of PD; verified its reliability by comparing it to existing signatures and combining several datasets. better ability to forecast.	(84)
Sekaran, 2023	Gene expression biomarkers (ORAI2, STIM1, TRPC3, TPI1 + other candidate genes)	GEO database (Accession: GSE36980). AD blood samples from frontal, hippocampal, and temporal regions vs. non-AD controls.	Supervised ML classifiers (Naive Bayes with 5-fold cross-validation, plus other ML algorithms; model interpretation with explainable AI)	100% accuracy Naive Bayes, 5-fold CV	Identified 34 (frontal), 60 (hippocampal), and 28 (temporal) genes as biomarkers. ORAI2 is present in all areas. Pathway analysis connected ORAI2 to STIM1 and TRPC3. Hub genes: TPI1, STIM1, TRPC3 → possible involvement in the development of AD. ML and AI together may help find medicinal targets.	(85)
Bhandari, 2023	Blood-based gene biomarkers	Gene Expression Omnibus (GEO) database (GSE6613, GSE72267, GSE99039, GSE57475, GSE18838)	Feature selection: LASSO, Ridge regression; Classification: Logistic Regression, SVM; Interpretation: SHAP (XAI)	All features were achieved above 80% accuracy.	Important blood-based gene biomarkers for PD found; some were also found in other NDDs; XAI made it easier to understand for early diagnosis.	(86)
Yu, 2024	Genetic biomarkers	Electroencephalography (EEG) signals, genotypes, and polygenic risk scores (PRSs)	Gradient Boosting (XGB), Random Forest (RF), Support Vector Machine (SVM)	Accuracy: 0.920; AUC: 0.916 (SVM)	The multimodal integration of EEG and genetic data facilitated excellent diagnosis accuracy, revealing substantial connections between EEG signals and clinical variables, with SVM being the most effective in differentiating AD from other disorders.	(87)

NDDs, neurodegenerative disorders; AD, Alzheimer's disease; PD, Parkinson's disease; ML, machine learning.

Table II. Machine learning-based discovery of molecular and cellular biomarkers in NDDs.

First author, year of publication	Biomarker type	Dataset	ML method	Accuracy	Key findings	Key limitations	(Refs.)
Bellomo, 2021	Core CSF biomarkers: Aβ42/40 ratio, p-tau, t-tau	Two large patient cohorts from AD biomarker centers	Unsupervised Gaussian mixture model clustering	Not specified	Classified patients into six clusters (AD-like and non-AD profiles); enabled computation of cluster-based cut-off values; improved data-driven stratification and phenotyping.	Cut-off values still influenced by group heterogeneity; external validation not reported; limited to CSF biomarkers only	(97)
Hallqvist, 2024	Blood protein panel (8 proteins: GRN, MASP2, BiP, PTGDS, ICAM1, C3, DKK3, SERPING1)	Recently diagnosed PD (n=99), pre-motor RBD cohorts (n=18 and n=54), healthy controls (n=36)	Discriminant OPLS-DA model	Classified and separated de novo PD or control samples with 100% accuracy based on the expression of eight proteins	A panel of eight blood protein biomarkers, using machine learning, differentiated early PD from controls, identified prodromal cases up to seven years before symptom onset, and showed promise for early risk stratification.	Relatively small pre-motor cohorts; needs external validation for clinical use.	(98)
Xu, 2022	Blood miRNA (serum and plasma profiles)	miRPathDB and GeneCards	Multilayer Perceptron (MLP) classifier, the Naive Bayes (NB) classifier, the Random Tree (RT) classifier, the Random Forest (RF) classifier, and the ZeroR (ZR) classifier in WEKA	The ZR and NB classifiers achieved an average accuracy of 80% in the cross-validation test, whereas RT achieved 82%, RF 86%, and MLP 92%.	By analyzing miRNA associated with AD, thousands of descriptors based on target genes and pathways were generated, which may subsequently be used to uncover new biomarkers and enhance disease detection.	Needs larger prospective validation; translational application not confirmed.	(99)
Kumar, 2024	Blood miRNAs (112 miRNAs: 56 PD biomarkers, 56 non-PD)	miRNAs were extracted from the miRpathDB database	Hoeffding Tree, Naive Bayes, Multilayer Perceptron, Sequential Model (Keras); best= Sequential Model	Identified miRNA biomarkers with 95.65% accuracy.	The created machine learning model using miRNAs their genomic route descriptors attained great accuracy in predicting Parkinson's disease.	Details limited to algorithm performance; requires larger independent validation; risk of overfitting from feature reduction.	(100)
Lin, 2020	Plasma protein biomarkers: Aβ42, Aβ40, total Tau, p-Tau181, α-synuclein	Plasma samples (*n*=377) from healthy controls, patients with AD spectrum (including mild cognitive impairment (MCI)), PD spectrum with variable cognitive	7 deep-learning classifiers (SVM, CART, C4.5, NB, LogReg, *k*NN, and RF and leave-one-out cross-validation (LOOCV) model.	76% (overall classification), 83% (AD subgroup severity), 63% (PD subgroup severity)	The constructed LDA model with the RF classifier may aid physicians in differentiating various NDDs.	The majority of patients were on pharmacological treatment, potentially influencing plasma protein profiles and impacting model precision; the control group was younger than the AD/PDD patients, so constraining comparability.	(101)

Table II. Continued.

First author, year of publication	Biomarker type	Dataset	ML method	Accuracy	Key findings	Key limitations	(Refs.)
		severity [including PD with dementia (PDD)], and FTD.					
Khorsand, 2025	Molecular biomarkers: neprilysin, alpha-secretase, beta-secretase, amyloid plaques, urinary formic acid	191 AD patients and 59 non-AD subjects	Naive Bayes (NB), Random Forest (RF), Decision Tree (DT), Support Vector Machine (SVM), and K-Nearest Neighbors (KNN)	KNN, SVM, RF, and DT achieved high sensitivity (94%) and accuracy (92%).	Targeted feature selection enhances diagnostic precision; biomarker-driven approaches distinguish AD from non-AD effectively.	Future research with bigger, longitudinal cohorts is crucial to better clarify these links and improve our comprehension of Alzheimer's processes, eventually seeking novel treatment methods.	(102)
Lam, 2022	Clinical biomarkers (alanine aminotransferase, alkaline phosphatase, bilirubin); Genetic biomarkers (SNPs)	1,223 UK Biobank participants (AD, PD, MND, MG)	Machine learning with Monte Carlo randomization; multinomial model	88.3% for NLD diagnosis using clinical markers	This research illustrates the efficacy of data-driven methodologies in discovering new biomarkers when no existing or potential biomarkers are available.	The multinomial model yielded results that contradicted current literature, including a negative coefficient for LDL in MND, suggesting reduced serum LDL levels in MND patients, which is inconsistent with prior findings. So, further research is required.	(103)
Yu, 2020	Protein-protein interaction (hub proteins)	Human interactome datasets from the I2D database	Random forest model, clustering algorithm MCODE	Prediction accuracy of 0.77 ± 0.01, AUC=0.86, and the validation set showed 77% accuracy.	Identified hub proteins essential in PPIN; potential NDD-related proteins; provides insights into disease pathogenesis.	Results need experimental validation.	(104)
Yang, 2024	Aging-related biomarkers (whole-blood RNA-Seq)	Training: 11 PD patients, 13 healthy controls; Validation: 3 GEO datasets + qRT-PCR on PBMCs (10 PD, 10 HC)	LASSO, Random Forest (RF), Support Vector Machine (SVM), Ridge Regression (RR)	Combined model AUC=0.98 (training); validation AUCs=0.833, 0.792, 0.725.	Found four aging-related genes that are strong diagnostic biomarkers; tested them in external datasets and PBMC samples; two biomarkers were linked to immune cell infiltration.	The training sample size is small (11 PD compared. 13 HC), and further testing is required in bigger groups.	(105)

NDDs, neurodegenerative disorders; AD, Alzheimer's disease; PD, Parkinson's disease; ML, machine learning.

Applications of machine learning in neuroimaging for early diagnosis

Developments in neuroimaging and ML have shown the ensured early detection of NDDs. CNNs have exhibited notale efficacy in detecting AD, with a 94.7% accuracy rate in distinguishing between early-stage AD and normal aging (106). Furthermore, DL and multimodal imaging analysis have created new avenues for using ML in different forms of dementia (107). Additionally, the ML-based analysis of single-photon emission computed tomography images has improved diagnostic precision and outperformed conventional techniques in identifying dopaminergic degradation in PD (108). Vieira *et al* (109) investigated ML and DL methods for identifying first-episode psychosis using neuroimaging data. Their findings revealed the variations in accuracy ranging from 50 to 70%, depending on the feature set. When DL was used with surface-based features, the greatest accuracy of 70% was obtained (109). It has been demonstrated that SVM and logistic regression are the optimal schizophrenia classifiers. More accurate than surface area, cortical thickness and subcortical volume align with the clinical severity and neurobiological patterns of schizophrenia (110). It has been demonstrated that ML can differentiate between AD, mild cognitive impairment (MCI) and healthy individuals by focusing on key brain areas such as the hippocampus. The accuracy rates are 66% for patients with MCI and 76% for AD compared to healthy controls (111). The ensemble transfer learning approach achieved an AUC of 90.2%, accurately differentiating AD from healthy individuals. Conversely, the lack of training images in the custom DL model led to its low performance. These results suggest that the use of transfer learning with neuroimages can enhance the early diagnosis and prognosis of AD, even when models are pre-trained on general images (112). The ML framework can be used to predict future cognitive categories in non-demented older adults. This suggests that using a baseline neuropsychiatric symptoms and mild behavioral impairment framework can improve the results (113). This approach drives research into dementia detection, optimizes resource utilization and improves clinical practice sensitivity.

In 2021, Murugan *et al* (114) introduced the DEMentia NETwork (DEMNET) for detecting dementia stages using MRI images. The model outperformed existing approaches on the Kaggle dataset with 95.23% accuracy, 97% AUC and 0.93 Cohen's Kappa. Additionally, the ability of the model to identify AD phases was tested using the ADNI dataset (114). In 2020, Jo *et al* (115) found that Tau PET images may be used to classify AD using a DL system that incorporates 3D CNN and LRP algorithms. This framework will also be useful for early identification during the prodromal stages of AD (115). The resting-state functional magnetic resonance imaging (fMRI) and DL approaches identify and diagnose AD throughout six phases. The FT network exhibited good accuracy throughout all phases, but the OTS network had the highest average accuracy of 97.92% (116). A summary of the performance metrics and clinical applications of FDA-approved AI/ML algorithms used in diagnosing NDDs is presented in Table III (117-125). These results indicate that combining fMRI with DL can enhance early diagnosis and improve the identification of risk factors and prognostic indicators.

7. Machine learning approaches in cognitive and behavioral assessment

ML is promising for cognitive and behavioral testing. In cognitive workload assessment, artificial neural networks and SVM accurately mimic physiological data (126). ML models based on previous functional analysis can improve the accuracy of indirect assessments such as the Questions About Behavioral Function (QABF), enhancing the identification of behavioral functions (127). Moreover, ML methods have been used to create robust personality assessment instruments using digital records and social media data, potentially enhancing personality theory when included in a thorough construct validation framework (128). Javed *et al* (129) designed the Cognitive Assessment of Smart Home Residents (CA-SHR) to assess daily functional health of elderly or cognitively impaired individuals using the internet of things. They used predetermined ratings and supervised classification to detect early cognitive impairment (129). Research has employed smart devices to automate test administration, speech transcription and clinical state prediction for frequent remote neuropsychological assessments, allowing for accurate evaluations of cognitive and emotional states and enabling continuous mental health monitoring (130). An active superior temporal sulcus predicted stop-signal reaction time well, accounting for 12% of the variation in multivariate ML research. This indicates how multivariate methods can boost brain function and performance knowledge (131). A supervised ML algorithm was previously used to predict the response to working memory training in patients with PD using demographic, clinical, cognitive and learning data. The use of training-inherent learning parameters improved the precision of the prediction models, potentially maximizing training benefits following cognitive interventions (132). Research has demonstrated that transdiagnostic factors strongly affect psychotic cognitive function. Psychosis-related cognitive impairment may reflect overall cognitive performance. A diagnosis-agnostic, symptom-targeted strategy may be suitable for evaluating therapies (133). The first validation research by Kim *et al* (134) revealed that virtual reality (VR) hand and eye motions may screen for MCI. SVM trained on virtual kiosk test data effectively discriminated patients with MCI from healthy controls, correlating these motions to cognitive domains and facilitating VR for MCI screening (Fig. 4) (134). These studies demonstrate the potential of ML in the enhancement of the accuracy and efficiency of cognitive and behavioral assessments.

8. Prediction of neurodegenerative diseases using multimodal integration

Multi-modal integration techniques have exhibited significant advantages in detecting NDDs. A novel methodology employs graph neural networks (GNNs) to integrate image and phenotypic data. Research has demonstrated the construction of brain networks from structural MRI (sMRI) or PET images within a multi-modal GNN framework. Experiments reveal that this method improves the diagnosis of AD, underscoring the need for comprehensive multi-modal diagnostic techniques (135). Lee *et al* (136) developed a multimodal recurrent neural network combining neuroimaging, CSF and cognitive

Table III. FDA-Approved AI/ML algorithms and neuroimaging-based studies for the diagnosis of NDDs.

Algorithm	Developer	Diseases	Modality used	Performance matrices	FDA approval date	Function of the algorithm	(Refs.)
Aidoc BriefCase-CSF triage	Aidoc Medical, Ltd.	Cervical Spine Fractures	cervical spine CT scans	Detection of Cervical Spine Fractures Sensitivity-54.9 Specificity-94.1 PPV-38.7 NPV-96.8	5/31/19	The system automatically alerts clinicians when a CT scan of the neck shows potential signs of a broken neck bone.	(117)
Vitrea CT Brain Perfusion	Vital Images, Inc.	Ischemic stroke	CT images	Detection of Ischemic Stroke Sensitivity-70.8 Specificity-80.0 PPV-98.8 NPV-10.2	11/20/18	Automatically computes quantitative brain perfusion metrics (rCBV, MTT, rCBF, TTP) from CT perfusion scans.	(118)
Health VCF	Zebra Medical Vision Ltd.	Vertebral fractures	CT images	Detection of VCFs Sensitivity-54.0 Specificity-92.0 PPV-69.0 NPV-87.0	5/12/20	Automatically detects and alerts on suspected intracranial hemorrhage (ICH) in CT scans; analyzes CT perfusion scans for stroke detection.	(119)
Syngo.CT Neuro Perfusion	Siemens Healthineers	Ischemic stroke	CT images	Detection of Ischemic Core Volumes Sensitivity-93.0-97.0 Specificity-97.0-100.0	10/11/20		(120)
Brainance MD	Advantis Medical Imaging	Major white matter tracts	MRI images	Detection of ICH Sensitivity-91.4 Specificity-97.5 PPV-80.2-97.3 NPV-91.9-99.0	10/14/21	Performs diffusion tensor imaging (DTI), dynamic susceptibility contrast (DSC) perfusion, and functional MRI (fMRI) analyses.	(121)
NeuroQuant	cortechs.ai	Alzheimer's disease	MRI images	Identification of Alzheimer's Sensitivity-63.0-88.5 Specificity-66.0-92.0	9/7/17	Processes volumetric MRI scans.	(122)
NeuroQuant	cortechs.ai	Mild cognitive impairment	MRI images	Identification of MCI Sensitivity-48.9-60.2 Specificity-80.0-80.6	9/7/17	Processes volumetric MRI scans.	(123,124)
Quantib Brain	Quantib BV	Dementia	MRI images	Diagnosis of Dementia Sensitivity-95.0-97.5 Specificity-60.0	3/9/18	Processes volumetric MRI scans.	(125)

NDDs, neurodegenerative disorders.

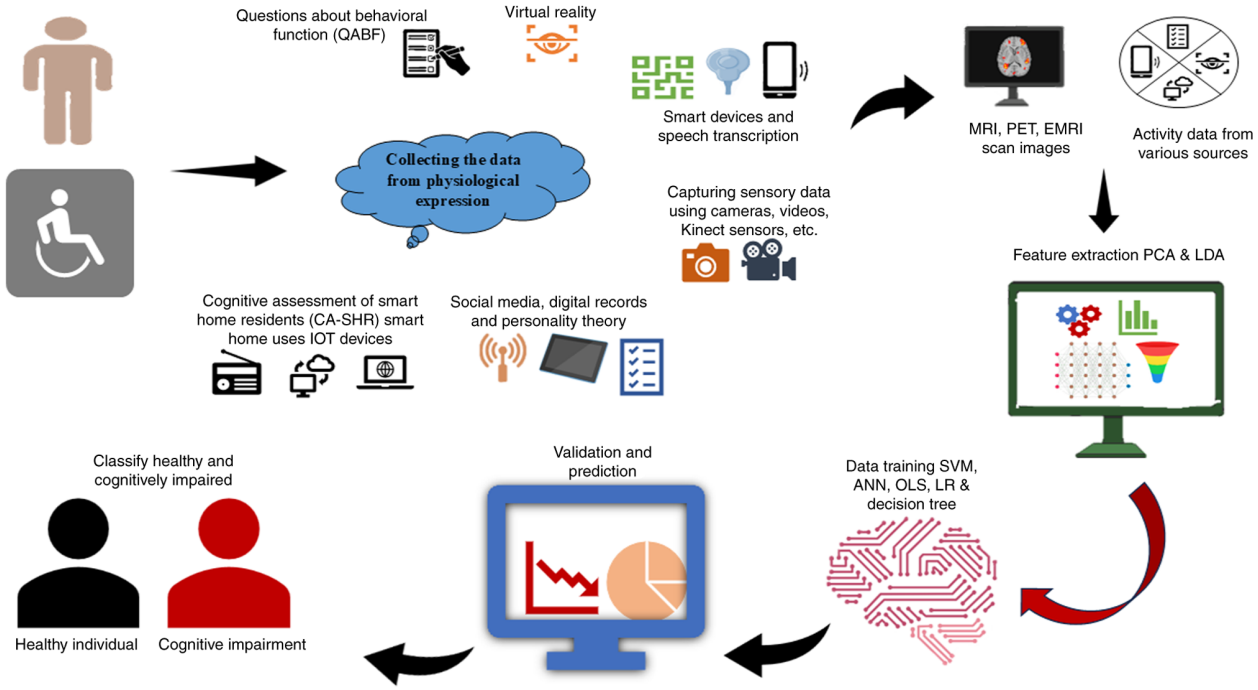

Figure 4. Schematic diagram illustrating how machine learning models are used in the early detection of cognitive and behavioral assessment. SVM, support vector machine; ANN, artificial neural network; OLS, ordinary least squares; LR, linear regression; MRI, magnetic resonance imaging; PET, positron emission tomography; FMRI, functional magnetic resonance imaging.

data to predict MCI progression to AD. Using longitudinal, multi-domain data, the model achieved 81% accuracy, aiding early risk identification and clinical trial selection (136). In their study, Liu *et al* (137) revealed the hierarchical attention-based multi-task multi-modal fusion model (HAMMF) designed to enhance AD diagnosis using multi-modal neuroimaging data, including MRI and PET images. Their results achieved an overall accuracy of 93.15% in differentiating between AD and healthy cases (137). Wang *et al* (138) introduced the hypergraph-regularized multimodal learning by the graph diffusion (HMGD) technique for the diagnosis of complex brain diseases. This method improves similarity metrics across participants by including imaging and genetic data (138). Employing a consolidated graph and a multi-kernel support vector machine (MK-SVM), HMGD exceeds current methodologies on ADNI data, uncovering substantial correlations and critical areas associated with genetic risk biomarkers for disease predictions.

The study by Zhu *et al* (139) developed a dynamic hyper-graph learning framework for multi-modal imaging-based computer-assisted diagnosis. The model estimates data representations and performs classification and regression tasks, promising to identify diagnostic labels and predict MCI and AD clinical scores (139). Castellano *et al* (140) examined multimodal models for 2D and 3D MRI and amyloid PET scan-based AD diagnosis. Volumetric data models outperform 2D images, and integrating imaging modalities increases prediction accuracy by focusing on Alzheimer's-related areas (140). By merging sMRI with resting-state functional MRI (rs-fMRI) data, the localized region extraction and multi-modal fusion (LRE-MMF) technique improves PD diagnosis. PCA separates imaging data into localized areas, identifies features, and decreases dimensionality, then processes them via a neural network to reach 75% accuracy, possibly enhancing diagnostic tools (141). Chen *et al* (142) described AD diagnosis using neuroimage-MED multimodal image feature fusion. This method improves classification and prediction, classifying AD, MCI and NC with 84.1% accuracy and predicting MCI development with 93.9%. Clinical diagnosis and neuroimaging bring the technique closer to clinical practice. This method is relatively new, with 86.95% of studies published over the past 5 years using data from biomedical imaging, cognitive assessments, speech and language evaluations, gait analysis, hand and eye movement tests, EEG and genetic evaluations (142). The study found that multimodal data categorization rates are sufficiently enough to distinguish AD, PD and MCI from healthy controls (143). Researchers use CNNs to extract features from MRI and PET brain imaging data to improve automated detection.

9. Conclusion and future directions

The present review emphasized the revolutionary potential of ML for the early identification and treatment of NDDs. The combination of numerous data sources, such as neuroimaging, genetic profiling, and biomarker analysis, has shown encouraging outcomes for improving diagnostic precision, recognizing disease risk factors, and facilitating personalized treatment approaches. The developments in ML approaches, particularly in processing high-dimensional data, represent a major leap forward in the capacity to predict disease progression and consequences. CNNs and multilayered models have made significant progress. This demonstrates that these technologies can accurately distinguish between different stages of illness and help clinicians to make decisions. However, despite these achievements, several problems persist.

Issues related to data standards, privacy, and the ethical implications of genetic testing require careful consideration and regulation. There is a greater need for longitudinal multimodal datasets that can more effectively document disease progression and diversity across various groups. Furthermore, the advancement of explainable ML techniques is crucial for enhancing transparency, interpretability, and clinical confidence in model predictions. The absence of defined biomarker techniques persists in hindering reproducibility and comparability across research, underscoring the need to create universal standards. Further study is required to verify the robustness and generalizability of ML models across varied demographics and clinical situations. Additionally, to fully utilize ML approaches in combating NDDs, multidisciplinary support among healthcare professionals, data scientists, and ethicists is necessary. A significant research gap exists in the application of machine learning discoveries from controlled research settings to practical clinical situations, necessitating collaboration among healthcare providers, data scientists, and ethicists. By bridging the gap between technology innovation and clinical application, researchers may advance toward a future of more precise, efficient and customized healthcare.

However, challenges and limitations remain. The use of ML in NDD research has considerable challenges. Limited and diverse datasets, particularly in rare NDDs, restrict model generalization and increase the risk of overfitting. Challenges such as missing data, inconsistent formats (such as neuroimaging, genetics and wearable sensor information), and difficulties in integrating multiple data types render model development more complex. A major obstacle is the lack of interpretability; many ML algorithms act as 'black boxes', which can reduce confidence among clinicians and patients. Additionally, the absence of standardized evaluation methods and technical hurdles for clinical implementation hinders real-world application. Ethical issues, including patient privacy, algorithmic bias, and ensuring equitable access, further contribute to these challenges. Addressing these challenges requires larger, high-quality datasets, advancements in explainable ML, the creation of standardized evaluation criteria, and thorough validation across multiple centers to build trust and ensure clinical use.

Acknowledgements

The authors would like to thank the management of Chettinad Academy of Research and Education (Deemed to be University), Chennai, India for providing the facilities to perform the present review.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

SV conducted the literature search, collected data, contributed to the writing of the manuscript, and created the tables and figures. SW performed the validation and curation of the data from the literature, and was involved in the revision process. LK was involved in the preparation of the manuscript and provided editing assistance. GKS conducted investigations, provided editing assistance and supervision, and conceptualized the study. All authors have thoroughly reviewed and approved the final manuscript. Data authentication is not applicable.

Ethics and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' information

The ORCID IDs of the authors are as follows: SV (0009-0004-1133-1646), SW (0000-0002-4703-0616), LK (0000-0002-3154-1331 and GKS (0000-0002-0531-424X).

References

1. Newell ME, Babbrah A, Aravindan A, Rathnam R, Kiernan R, Driver EM, Bowes DA and Halden RU: Prevalence rates of neurodegenerative diseases versus human exposures to heavy metals across the United States. Sci Total Environ 928: 172260, 2024.
2. Adams JL, Myers TL, Waddell EM, Spear KL and Schneider RB: Telemedicine: A valuable tool in neurodegenerative diseases. Curr Geriatr Rep 9: 72-81, 2020.
3. Hansson O: Biomarkers for neurodegenerative diseases. Nat Med 27: 954-963, 2021.
4. Better MA: 2023 Alzheimer's disease facts and figures. Alzheimers Dement 19: 1598-1695, 2023.
5. Bhidayasiri R, Sringean J, Phumphid S, Anan C, Thanawattano C, Deoisres S, Panyakaew P, Phokaewvarangkul O, Maytharakcheep S, Buranasrikul V and Prasertpan T: The rise of Parkinson's disease is a global challenge, but efforts to tackle this must begin at a national level: A protocol for national digital screening and 'eat, move, sleep' lifestyle interventions to prevent or slow the rise of non-communicable diseases in Thailand. Front Neurol 15: 1386608, 2024.
6. Mead RJ, Shan N, Reiser HJ, Marshall F and Shaw PJ: Amyotrophic lateral sclerosis: A neurodegenerative disorder poised for successful therapeutic translation. Nat Rev Drug Discov 22: 185-1212, 2023.
7. Bloem BR, Okun MS and Klein C: Parkinson's disease. Lancet 397: 2284-2303, 2021.
8. Baker E, Leonenko G, Schmidt KM, Hill M, Myers AJ, Shoai M, de Rojas I, Tesi N, Holstege H, van der Flier WM and Pijnenburg YA: What does heritability of Alzheimer's disease represent? PLoS One 18: e0281440, 2023.
9. Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D, Tan M, Kia DA, Noyce AJ, Xue A and Bras J: Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: A Meta-analysis of Genome-wide association studies. Lancet Neurol 18: 1091-1102, 2019.
10. Sakowski SA, Koubek EJ, Chen KS, Goutman SA and Feldman EL: Role of the exposome in neurodegenerative disease: Recent insights and future directions. Ann Neurol 95: 635-652, 2024.
11. Rekatsina M, Paladini A, Piroli A, Zis P, Pergolizzi JV and Varrassi G: Pathophysiology and therapeutic perspectives of oxidative stress and neurodegenerative diseases: A narrative review. Adv Ther 37: 113-139, 2020.

12. Cravello L, Di Santo S, Varrassi G, Benincasa D, Marchettini P, de Tommaso M, Shofany J, Assogna F, Perotta D, Palmer K and Paladini A: Chronic pain in the elderly with cognitive decline: A narrative review. Pain Ther 8: 53-65, 2019.
13. Aldharman SS, Al-Jabr KH, Alharbi YS, Alnajar NK, Alkhanani JJ, Alghamdi A, Abdellatif RA, Allouzi A, Almallah AM and Jamil SF: Implications of early diagnosis and intervention in the management of Neurodevelopmental Delay (NDD) in children: A systematic review and Meta-analysis. Cureus 15: e38745, 2023.
14. Mobed A and Hasanzadeh M: Biosensing: The best alternative for conventional methods in detection of Alzheimer's disease biomarkers. Int J Biol Macromol 161: 59-71, 2020.
15. Selvam S and Ayyavoo V: Biomarkers in neurodegenerative diseases: A broad overview. Exploration Neuroprotective Ther 4: 119-147, 2024.
16. Rastogi S, Sharma V, Bharti PS, Rani K, Modi GP, Nikolajeff F and Kumar S: The evolving landscape of exosomes in neurodegenerative diseases: Exosomes characteristics and a promising role in early diagnosis. Int J Mol Sci 22: 440, 2021.
17. Dubois B, von Arnim CA, Burnie N, Bozeat S and Cummings J: Biomarkers in Alzheimer's disease: Role in early and differential diagnosis and recognition of atypical variants. Alzheimers Res Ther 15: 175, 2023.
18. Chudzik A, Śledzianowski A and Przybyszewski AW: Machine learning and digital biomarkers can detect early stages of neurodegenerative diseases. Sensors 24: 1572, 2024.
19. Dorsey ER, Papapetropoulos S, Xiong M and Kieburtz K: The first frontier: Digital biomarkers for neurodegenerative disorders. Digital Biomarkers 1: 6-13, 2017.
20. Iftikhar M, Saqib M, Zareen M and Mumtaz H: Artificial intelligence: Revolutionizing robotic surgery. Ann Med Surg (Lond) 86: 5401-5409, 2024.
21. Bajwa J, Munir U, Nori A and Williams B: Artificial intelligence in healthcare: Transforming the practice of medicine. Future Healthc J 8: e188-e194, 2021.
22. García-Fonseca Á, Martin-Jimenez C, Barreto GE, Pachón AF and González J: The emerging role of long non-coding RNAs and microRNAs in neurodegenerative diseases: A perspective of machine learning. Biomolecules 11: 1132, 2021.
23. Khaliq F, Oberhauser J, Wakhloo D and Mahajani S: Decoding degeneration: The implementation of machine learning for clinical detection of neurodegenerative disorders. Neural Regen Res 18: 1235-1242, 2023.
24. DeTure MA and Dickson DW: The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegener 14: 32, 2019.
25. Sheppard O and Coleman M: Alzheimer's disease: Etiology, neuropathology and pathogenesis. Exon Publications 19: 1-21, 2020.
26. García-Morales V, González-Acedo A, Melguizo-Rodríguez L, Pardo-Moreno T, Costela-Ruiz VJ, Montiel-Troya M and Ramos-Rodríguez JJ: Current understanding of the physiopathology, diagnosis and therapeutic approach to Alzheimer's disease. Biomedicines 9: 1910, 2021.
27. Tiwari S, Atluri V, Kaushik A, Yndart A and Nair M: Alzheimer's disease: Pathogenesis, diagnostics, and therapeutics. Int J Nanomedicine 14: 5541-5554, 2019.
28. Riederer P, Berg D, Casadei N, Cheng F, Classen J, Dresel C, Jost W, Krüger R, Müller T, Reichmann H, *et al*: α-Synuclein in Parkinson's disease: Causal or bystander? J Neural Transm (Vienna) 126: 815-840, 2019.
29. Masato A, Plotegher N, Terrin F, Sandre M, Faustini G, Thor A, Adams S, Berti G, Cogo S, De Lazzari F and Fontana CM: DOPAL Initiates αSynuclein-dependent impaired proteostasis and degeneration of neuronal projections in Parkinson's disease. NPJ Parkinsons Dis 9: 42, 2023.
30. Simpson C, Vinikoor-Imler L, Nassan FL, Shirvan J, Lally C, Dam T and Maserejian N: Prevalence of ten LRRK2 variants in Parkinson's disease: A comprehensive review. Parkinsonism Relat Disord 98: 103-113, 2022.
31. Zhou ZD, Yi LX, Wang DQ, Lim TM and Tan EK: Role of dopamine in the pathophysiology of Parkinson's disease. Transl Neurodegener 12: 44, 2023.
32. Calabresi P, Mechelli A, Natale G, Volpicelli-Daley L, Di Lazzaro G and Ghiglieri V: Alpha-synuclein in Parkinson's disease and other synucleinopathies: From overt neurodegeneration back to early synaptic dysfunction. Cell Death Dis 14: 176, 2023.
33. Zhou W and Xu R: Current insights in the molecular genetic pathogenesis of amyotrophic lateral sclerosis. Front Neurosci 17: 1189470, 2023.
34. Liu J and Wang F: Role of neuroinflammation in amyotrophic lateral sclerosis: Cellular mechanisms and therapeutic implications. Front Immunol 8: 1005, 2017.
35. Masrori P and Van Damme P: Amyotrophic lateral sclerosis: A clinical review. Eur J Neurol 27: 1918-1929, 2020.
36. Semmler S, Gagné M, Garg P, Pickles SR, Baudouin C, Hamon-Keromen E, Destroismaisons L, Khalfallah Y, Chaineau M, Caron E and Bayne AN: TNF receptor-associated factor 6 interacts with ALS-linked misfolded superoxide dismutase 1 and promotes aggregation. J Biol Chem 295: 3808-3825, 2020.
37. Farrawell NE and Yerbury JJ: Mutant Cu/Zn superoxide dismutase (A4V) turnover is altered in cells containing inclusions. Front Mol Neurosci 14: 771911, 2021.
38. Tedesco B, Ferrari V, Cozzi M, Chierichetti M, Casarotto E, Pramaggiore P, Mina F, Galbiati M, Rusmini P, Crippa V and Cristofani R: The role of small heat shock proteins in protein misfolding associated motoneuron diseases. Int J Mol Sci 23: 11759, 2022.
39. Maurel C, Dangoumau A, Marouillat S, Brulard C, Chami A, Hergesheimer R, Corcia P, Blasco H, Andres CR and Vourc'h P: Causative genes in amyotrophic lateral sclerosis and protein degradation pathways: A link to neurodegeneration. Mol Neurobiol 55: 6480-6499, 2018.
40. Bottero V, Santiago JA, Quinn JP and Potashkin JA: Key disease mechanisms linked to amyotrophic lateral sclerosis in spinal cord motor neurons. Front Mol Neurosci 15: 825031, 2022.
41. Dokholyan NV, Mohs RC and Bateman RJ: Challenges and progress in research, diagnostics, and therapeutics in Alzheimer's disease and related dementias. Alzheimers Dement (N Y) 8: e12330, 2022.
42. Domínguez-Fernández C, Egiguren-Ortiz J, Razquin J, Gómez-Galán M, De las Heras-García L, Paredes-Rodríguez E, Astigarraga E, Miguélez C and Barreda-Gómez G: Review of technological challenges in personalised medicine and early diagnosis of neurodegenerative disorders. Int J Mol Sci 24: 3321, 2023.
43. Shusharina N, Yukhnenko D, Botman S, Sapunov V, Savinov V, Kamyshov G, Sayapin D and Voznyuk I: Modern methods of diagnostics and treatment of neurodegenerative diseases and depression. Diagnostics (Basel) 13: 573, 2023.
44. Anique M, Talib M, Ihsan A, Anwar I, Zeeshan A and Ahsan N: Biomarker profiles in serum and CSF for early diagnosis of selected neurodegenerative diseases: Serum and CSF for early diagnosis of neurodegenerative diseases. Pakistan J Health Sci 5: 166-70, 2024.
45. Kammeyer R, Chapman K, Furniss A, Hsieh E, Fuhlbrigge R, Ogbu EA, Boackle S, Zell J, Nair KV, Borko TL, *et al*: Blood-based biomarkers of neuronal and glial injury in active major neuropsychiatric systemic lupus erythematosus. Lupus 33: 1116-1129, 2024.
46. Koníčková D, Menšíková K, Tučková L, Hényková E, Strnad M, Friedecký D, Stejskal D, Matěj R and Kaňovský P: Biomarkers of neurodegenerative diseases: Biology, taxonomy, clinical relevance, and current research status. Biomedicines 10: 1760, 2022.
47. Hansson O, Lehmann S, Otto M, Zetterberg H and Lewczuk P: Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease. Alzheimers Res Ther 11: 34, 2019.
48. Feng Y, Murphy MC, Hojo E, Li F and Roberts N: Magnetic resonance elastography in the study of neurodegenerative diseases. J Magn Reson Imaging 59: 82-96, 2024.
49. Young PN, Estarellas M, Coomans E, Srikrishna M, Beaumont H, Maass A, Venkataraman AV, Lissaman R, Jiménez D, Betts MJ, *et al*: Imaging biomarkers in neurodegeneration: Current and future practices. Alzheimers Res Ther 12: 49, 2020.
50. Myrou A, Barmpagiannos K, Ioakimidou A and Savopoulos C: Molecular biomarkers in neurological diseases: Advances in diagnosis and prognosis. Int J Mol Sci 26: 2231, 2025.
51. Ni A and Sethi A; Alzheimer's disease Neuroimaging Initiative: Functional genetic biomarkers of Alzheimer's disease and gene expression from peripheral blood. bioRxiv. Jan 18, 2021 doi: 10.1101/2021.01.15.426891.
52. Abbas S, Asif M, Rehman A, Alharbi M, Khan MA and Elmitwally N: Emerging research trends in artificial intelligence for cancer diagnostic systems: A comprehensive review. Heliyon 10: e36743, 2024.

53. Alowais SA, Alghamdi SS, Alsuhebany N, Alqahtani T, Alshaya AI, Almohareb SN, Aldairem A, Alrashed M, Bin Saleh K, Badreldin HA, *et al*: Revolutionizing healthcare: The role of artificial intelligence in clinical practice. BMC Med Educ 23: 689, 2023.
54. Sidey-Gibbons JA and Sidey-Gibbons CJ: Machine learning in medicine: A practical introduction. BMC Med Res Methodol 19: 1-8, 2019.
55. Mirnezami R, Nicholson J and Darzi A: Preparing for precision medicine. N Engl J Med 366: 489-491, 2012.
56. Ibrahim IM and Abdulazeez AM: The role of machine learning algorithms for diagnosing diseases. Learning 4: 6, 2021.
57. Saputra NA, Riza LS, Setiawan A and Hamidah I: A systematic review for classification and selection of deep learning methods. Decision Analytics J 12: 100489, 2024.
58. Labory J, Njomgue-Fotso E and Bottini S: Benchmarking feature selection and feature extraction methods to improve the performances of machine-learning algorithms for patient classification using metabolomics biomedical data. Comput Struct Biotechnol J 23: 1274-1287, 2024.
59. Jia W, Sun M, Lian J and Hou S: Feature dimensionality reduction: A review. Complex Intelligent Systems 8: 2663-2693, 2022.
60. Sarder MA, Maniruzzaman M and Ahammed B: Feature selection and classification of leukemia cancer using machine learning techniques. Machine Learning Res 5: 18, 2020.
61. Remeseiro B and Bolon-Canedo V: A review of feature selection methods in medical applications. Comput Biol Med 112: 103375, 2019.
62. Harrison CJ and Sidey-Gibbons CJ: Machine learning in medicine: A practical introduction to natural language processing. BMC Med Res Methodol 21: 158, 2021.
63. Pfob A, Lu SC and Sidey-Gibbons C: Machine learning in medicine: A practical introduction to techniques for data pre-processing, hyperparameter tuning, and model comparison. BMC Med Res Methodol 22: 282, 2022.
64. Samala RK, Chan HP, Hadjiiski L and Helvie MA: Risks of feature leakage and sample size dependencies in deep feature extraction for breast mass classification. Medical Physics 48: 2827-2837, 2021.
65. Varoquaux G and Colliot O: Evaluating machine learning models and their diagnostic value. In: Machine Learning for Brain Disorders [Internet]. New York, NY, Humana, 2023.
66. Erickson BJ and Kitamura F: Magician's corner: 9. Performance metrics for machine learning models. Radiol Artif Intell 3: e200126, 2021.
67. Handelman GS, Kok HK, Chandra RV, Razavi AH, Huang S, Brooks M, Lee MJ and Asadi H: Peering into the black box of artificial intelligence: Evaluation metrics of machine learning methods. Am J Roentgenol 212: 38-43, 2019.
68. Hicks SA, Strümke I, Thambawita V, Hammou M, Riegler MA, Halvorsen P and Parasa S: On evaluation metrics for medical applications of artificial intelligence. Sci Rep 12: 5979, 2022.
69. Ledesma D, Symes S and Richards S: Advancements within modern machine learning methodology: Impacts and prospects in biomarker discovery. Curr Med Chem 28: 6512-6531, 2021.
70. Lam S, Arif M, Song X, Uhlen M and Mardinoglu A: Machine learning analysis reveals biomarkers for the detection of neurodegenerative diseases. medRxiv. Feb 15, 2022.
71. Arisi I, D'Onofrio M, Brandi R, Sonnessa M, Campanelli A, Florio R, Sposato V, Malerba F, Cattaneo A, Mecocci P and Bruno G: Mining clinical and laboratory data of neurodegenerative diseases by machine learning: Transcriptomic biomarkers. In 2018 IEEE International Conference on Bioinformatics and Biomedicine (BIBM), IEEE, pp2735-2737, Dec 3, 2018.
72. Li Z, Guo W, Ding S, Chen L, Feng K, Huang T and Cai YD: Identifying key MicroRNA signatures for neurodegenerative diseases with machine learning methods. Front Genet 13: 880997, 2022.
73. Huseby CJ, Delvaux E, Brokaw DL and Coleman PD: Blood transcript biomarkers selected by machine learning algorithm classify neurodegenerative diseases including Alzheimer's disease. Biomolecules 12: 1592, 2022.
74. Ren J, Zhang B, Wei D and Zhang Z: Identification of methylated gene biomarkers in patients with Alzheimer's disease based on machine learning. Biomed Res Int 2020: 8348147, 2020.
75. Abd El Hamid MM, Mabrouk MS and Omar YM: Developing an early predictive system for identifying genetic biomarkers associated to Alzheimer's disease using machine learning techniques. Biomed Engineering Applications Basis Communications 31: 1950040, 2019.
76. Kelly J, Moyeed R, Carroll C, Luo S and Li X: Blood biomarker-based classification study for neurodegenerative diseases. Sci Rep 13: 17191, 2023.
77. Abdelwahab MM, Al-Karawi KA and Semary HE: Deep learning-based prediction of Alzheimer's disease using microarray gene expression data. Biomedicines 11: 3304, 2023.
78. Wang Y, Wu D, Zheng M and Yang T: An integrated bioinformatics and machine learning approach to identifying biomarkers connecting Parkinson's disease with purine metabolism-related genes. BMC Neurol 25: 161, 2025.
79. Huang Y, Sun X, Jiang H, Yu S, Robins C, Armstrong MJ, Li R, Mei Z, Shi X, Gerasimov ES and De Jager PL: A machine learning approach to brain epigenetic analysis reveals kinases associated with Alzheimer's disease. Nat Commun 12: 4472, 2021.
80. Alamro H, Thafar MA, Albaradei S, Gojobori T, Essack M and Gao X: Exploiting machine learning models to identify novel Alzheimer's disease biomarkers and potential targets. Sci Rep 13: 4979, 2023.
81. Madar IH, Sultan G, Tayubi IA, Hasan AN, Pahi B, Rai A, Sivanandan PK, Loganathan T, Begum M and Rai S: Identification of marker genes in Alzheimer's disease using a machine-learning model. Bioinformation 17: 348-355, 2021.
82. Lin RH, Wang CC and Tung CW: A machine learning classifier for predicting stable MCI patients using gene biomarkers. Int J Environ Res Public Healt 19: 4839, 2022.
83. Sharma A and Dey P: A machine learning approach to unmask novel gene signatures and prediction of Alzheimer's disease within different brain regions. Genomics 113: 1778-1789, 2021.
84. Augustine J and Jereesh AS: Blood-based gene-expression biomarkers identification for the non-invasive diagnosis of Parkinson's disease using two-layer hybrid feature selection. Gene 823: 146366, 2022.
85. Sekaran K, Alsamman AM, George Priya Doss C and Zayed H: Bioinformatics investigation on blood-based gene expressions of Alzheimer's disease revealed ORAI2 gene biomarker susceptibility: An explainable artificial intelligence-based approach. Metabolic Brain Disease 38: 1297-1310, 2023.
86. Bhandari N, Walambe R, Kotecha K and Kaliya M: Integrative gene expression analysis for the diagnosis of Parkinson's disease using machine learning and explainable AI. Comput Biol Med 163: 107140, 2023.
87. Yu WY, Sun TH, Hsu KC, Wang CC, Chien SY, Tsai CH and Yang YW: Comparative analysis of machine learning algorithms for Alzheimer's disease classification using EEG signals and genetic information. Comput Biol Med 176: 108621, 2024.
88. Shi K, Lin W and Zhao XM: Identifying molecular biomarkers for diseases with machine learning based on integrative omics. IEEE/ACM Trans Comput Biol Bioinform 18: 2514-2525, 2020.
89. Brar A, Zhu A, Baciu C, Sharma D, Xu W, Orchanian-Cheff A, Wang B, Reimand J, Grant R and Bhat M: Development of diagnostic and prognostic molecular biomarkers in hepatocellular carcinoma using machine learning: A systematic review. Liver Cancer International 3: 141-161, 2022.
90. Mertins SD: Capturing biomarkers and molecular targets in cellular landscapes from dynamic reaction network models and machine learning. Front Oncol 11: 805592, 2022.
91. Macyszyn L, Akbari H, Pisapia JM, Da X, Attiah M, Pigrish V, Bi Y, Pal S, Davuluri RV, Roccograndi L and Dahmane N: Imaging patterns predict patient survival and molecular subtype in glioblastoma via machine learning techniques. Neuro Oncol 18: 417-425, 2015.
92. Wang J, Kang Z, Liu Y, Li Z, Liu Y and Liu J: Identification of immune cell infiltration and diagnostic biomarkers in unstable atherosclerotic plaques by integrated bioinformatics analysis and machine learning. Front Immunol 13: 956078, 2022.
93. Liang Y, Lin F and Huang Y: Identification of biomarkers associated with diagnosis of osteoarthritis patients based on bioinformatics and machine learning. J Immunol Res 2022: 5600190, 2022.
94. Sinkala M, Mulder N and Martin D: Machine learning and network analyses reveal disease subtypes of pancreatic cancer and their molecular characteristics. Sci Rep 10: 1212, 2020.
95. Zheng H, Zhang Q, Gong Y, Liu Z and Chen S: Identification of prognostic biomarkers for stage iii non-small cell lung carcinoma in female nonsmokers using machine learning. arXiv: Aug 28, 2024.
96. Rydzewski NR, Helzer KT, Bootsma M, Shi Y, Bakhtiar H, Sjöström M and Zhao SG: Machine learning & molecular radiation tumor biomarkers. Semin Radiat Oncol 33: 243-251, 2023.

97. Bellomo G, Indaco A, Chiasserini D, Maderna E, Paolini Paoletti F, Gaetani L, Paciotti S, Petricciuolo M, Tagliavini F, Giaccone G and Parnetti L: Machine learning driven profiling of cerebrospinal fluid core biomarkers in Alzheimer's disease and other neurological disorders. Front Neurosci 15: 647783, 2021.
98. Hallqvist J, Bartl M, Dakna M, Schade S, Garagnani P, Bacalini MG, Pirazzini C, Bhatia K, Schreglmann S, Xylaki M and Weber S: Plasma proteomics identify biomarkers predicting Parkinson's disease up to 7 years before symptom onset. Nat Commun 15: 4759, 2024.
99. Xu A, Kouznetsova VL and Tsigelny IF: Alzheimer's disease diagnostics using mirna biomarkers and machine learning. J Alzheimers Dis 86: 841-859, 2022.
100. Kumar A, Kouznetsova VL, Kesari S and Tsigelny IF: Parkinson's disease diagnosis using miRNA biomarkers and deep learning. Front Biosci (Landmark Ed) 29: 4, 2024.
101. Lin CH, Chiu SI, Chen TF, Jang JS and Chiu MJ: Classifications of neurodegenerative disorders using a multiplex blood biomarkers-based machine learning model. Int J Mol Sci 21: 6914, 2020.
102. Khorsand B, Salehi S, Karimi S, Karimipasand S, Fariborzi N, Houri H and Asri N: Investigating Alzheimer's disease biomarkers by applying machine learning models. bioRxiv: Mar 21, 2025 doi: 10.1101/2025.03.19.643368.
103. Lam S, Arif M, Song X, Uhlén M and Mardinoglu A: Machine learning analysis reveals biomarkers for the detection of neurological diseases. Front Mol Neurosci 15: 889728, 2022.
104. Yu X, Lai S, Chen H and Chen M: Protein-protein interaction network with machine learning models and multiomics data reveal potential neurodegenerative disease-related proteins. Hum Mol Genet 29: 1378-1387, 2020.
105. Yang W, Xu S, Zhou M and Chan P: Aging-related biomarkers for the diagnosis of Parkinson's disease based on bioinformatics analysis and machine learning. Aging (Albany NY) 16: 12191, 2024.
106. Mohammed EM, Fakhrudeen AM and Alani OY: Detection of Alzheimer's disease using deep learning models: A systematic literature review. Informatics Med Unlocked 50: 101551, 2024.
107. Myszczynska MA, Ojamies PN, Lacoste AM, Neil D, Saffari A, Mead R, Hautbergue GM, Holbrook JD and Ferraiuolo L: Applications of machine learning to diagnosis and treatment of neurodegenerative diseases. Nat Rev Neurol 16: 440-456, 2020.
108. Ahmed MR, Zhang Y, Feng Z, Lo B, Inan OT and Liao H: Neuroimaging and machine learning for dementia diagnosis: Recent advancements and future prospects. IEEE Rev Biomed Eng 12: 19-33, 2018.
109. Vieira S, Gong QY, Pinaya WH, Scarpazza C, Tognin S, Crespo-Facorro B, Tordesillas-Gutierrez D, Ortiz-García V, Setien-Suero E, Scheepers F, *et al*: Using machine learning and structural neuroimaging to detect first episode psychosis: Reconsidering the evidence. Schizophr Bull 46: 17-26, 2020.
110. Yassin W, Nakatani H, Zhu Y, Kojima M, Owada K, Kuwabara H, Gonoi W, Aoki Y, Takao H, Natsubori T, *et al*: Machine-learning classification using neuroimaging data in schizophrenia, autism, ultra-high risk and first-episode psychosis. Transl Psychiatry 10: 278, 2020.
111. Salvatore C, Cerasa A, Battista P, Gilardi MC, Quattrone A and Castiglioni I; Alzheimer's Disease Neuroimaging Initiative: Magnetic resonance imaging biomarkers for the early diagnosis of Alzheimer's disease: A machine learning approach. Front Neurosci 9: 307, 2015.
112. Nanni L, Interlenghi M, Brahnam S, Salvatore C, Papa S, Nemni R and Castiglioni I; Alzheimer's Disease Neuroimaging Initiative: Comparison of transfer learning and conventional machine learning applied to structural brain MRI for the early diagnosis and prognosis of Alzheimer's disease. Front Neurol 11: 576194, 2020.
113. Gill S, Mouches P, Hu S, Rajashekar D, MacMaster FP, Smith EE, Forkert ND and Ismail Z; Alzheimer's disease neuroimaging initiative: Using machine learning to predict dementia from neuropsychiatric symptom and neuroimaging data. J Alzheimers Dis 75: 277-288, 2020.
114. Murugan S, Venkatesan C, Sumithra MG, Gao XZ, Elakkiya B, Akila M and Manoharan S: DEMNET: A deep learning model for early diagnosis of Alzheimer diseases and dementia from MR images. Ieee Access 9: 90319-90329, 2021.
115. Jo T, Nho K, Risacher SL and Saykin AJ; Alzheimer's Neuroimaging Initiative: Deep learning detection of informative features in tau PET for Alzheimer's disease classification. BMC Bioinformatics 21 (Suppl 21): S496, 2020.
116. Ramzan F, Khan MU, Rehmat A, Iqbal S, Saba T, Rehman A and Mehmood Z: A deep learning approach for automated diagnosis and multi-class classification of Alzheimer's disease stages using resting-state fMRI and residual neural networks. J Med Syst 44: 37, 2019.
117. Voter AF, Larson ME, Garrett JW and Yu JP: Diagnostic accuracy and failure mode analysis of a deep learning algorithm for the detection of cervical spine fractures. AJNR Am J Neuroradiol 42: 1550-1556, 2021.
118. Rava RA, Snyder KV, Mokin M, Waqas M, Allman AB, Senko JL, Podgorsak AR, Bhurwani MS, Hoi Y, Siddiqui AH, *et al*: Assessment of a Bayesian Vitrea CT perfusion analysis to predict final infarct and penumbra volumes in patients with acute ischemic stroke: A comparison with RAPID. AJNR Am J Neuroradiol 41: 206-212, 2020.
119. Kolanu N, Silverstone EJ, Ho BH, Pham H, Hansen A, Pauley E, Quirk AR, Sweeney SC, Center JR and Pocock NA: Clinical utility of computer-aided diagnosis of vertebral fractures from computed tomography images. J Bone Miner Res 35: 2307-2312, 2020.
120. Koopman MS, Berkhemer OA, Geuskens RR, Emmer BJ, van Walderveen MA, Jenniskens SF, van Zwam WH, van Oostenbrugge RJ, van der Lugt A, Dippel DW, *et al*: Comparison of three commonly used CT perfusion software packages in patients with acute ischemic stroke. J Neurointerv Surg 11: 1249-1256, 2019.
121. Christidi F, Karavasilis E, Samiotis K, Bisdas S and Papanikolaou N: Fiber tracking: A qualitative and quantitative comparison between four different software tools on the reconstruction of major white matter tracts. Eur J Radiol Open 3: 153-161, 2016.
122. Persson K, Barca ML, Cavallin L, Brækhus A, Knapskog AB, Selbæk G and Engedal K: Comparison of automated volumetry of the hippocampus using NeuroQuant® and visual assessment of the medial temporal lobe in Alzheimer's disease. Acta Radiol 59: 997-1001, 2018.
123. Kwon C, Kang KM, Byun MS, Yi D, Song H, Lee JY, Hwang I, Yoo RE, Yun TJ, Choi SH, *et al*: Assessment of mild cognitive impairment in elderly subjects using a fully automated brain segmentation software. Invest Magnetic Resonance Imaging 25: 164-171, 2021.
124. Persson K, Selbæk G, Brækhus A, Beyer M, Barca M and Engedal K: Fully automated structural MRI of the brain in clinical dementia workup. Acta Radiol 58: 740-747, 2017.
125. Zaki LA, Vernooij MW, Smits M, Tolman C, Papma JM, Visser JJ and Steketee RM: Comparing two artificial intelligence software packages for normative brain volumetry in memory clinic imaging. Neuroradiology 64: 1359-1366, 2022.
126. Elkin C, Nittala S and Devabhaktuni V: Fundamental cognitive workload assessment: A machine learning comparative approach. In: Advances in Neuroergonomics and Cognitive Engineering: Proceedings of the AHFE 2017 International Conference on Neuroergonomics and Cognitive Engineering, July 17-21, 2017, The Westin Bonaventure Hotel, Springer International Publishing, Los Angeles, CA, pp275-284, 2018.
127. Bailey JD, Baker JC, Rzeszutek MJ and Lanovaz MJ: Machine learning for supplementing behavioral assessment. Perspect Behav Sci 44: 605-619, 2021.
128. Bleidorn W and Hopwood CJ: Using machine learning to advance personality assessment and theory. Pers Soc Psychol Rev 23: 190-203, 2019.
129. Javed AR, Fahad LG, Farhan AA, Abbas S, Srivastava G, Parizi RM and Khan MS: Automated cognitive health assessment in smart homes using machine learning. Sustainable Cities Soc 65: 102572, 2021.
130. Chandler C, Foltz PW, Cohen AS, Holmlund TB, Cheng J, Bernstein JC, Rosenfeld EP and Elvevåg B: Machine learning for ambulatory applications of neuropsychological testing. Intelligence Based Med 1: 100006, 2020.
131. Yuan D, Hahn S, Allgaier N, Owens MM, Chaarani B, Potter A and Garavan H: Machine learning approaches linking brain function to behavior in the ABCD STOP task. Hum Brain Mapp 44: 1751-1766, 2023.
132. Ophey A, Wenzel J, Paul R, Giehl K, Rehberg S, Eggers C, Reker P, van Eimeren T, Kalbe E and Kambeitz-Ilankovic L: Cognitive performance and learning parameters predict response to working memory training in Parkinson's disease. J Surg Case Rep 12: 2235-2247, 2022.
133. McCutcheon RA, Keefe RS, McGuire PM and Marquand A: Deconstructing cognitive impairment in psychosis with a machine learning approach. JAMA Psychiatry 82: 57-65, 2025.

134. Kim SY, Park J, Choi H, Loeser M, Ryu H and Seo K: Digital marker for early screening of mild cognitive impairment through hand and eye movement analysis in virtual reality using machine learning: First validation study. J Med Internet Res 25: e48093, 2023.
135. Zhang Y, He X, Chan YH, Teng Q and Rajapakse JC: Multi-modal graph neural network for early diagnosis of Alzheimer's disease from sMRI and PET scans. Comput Biol Med 164: 107328, 2023.
136. Lee G, Nho K, Kang B, Sohn KA and Kim D: Predicting Alzheimer's disease progression using multi-modal deep learning approach. Sci Rep 9: 1952, 2019.
137. Liu X, Li W, Miao S, Liu F, Han K and Bezabih TT: HAMMF: Hierarchical attention-based multi-task and multi-modal fusion model for computer-aided diagnosis of Alzheimer's disease. Comput Biol Med 176: 108564, 2024.
138. Wang M, Shao W, Huang S and Zhang D: Hypergraph-regularized multimodal learning by graph diffusion for imaging genetics based alzheimer's disease diagnosis. Med Image Anal 89: 102883, 2023.
139. Zhu Y, Zhu X, Kim M, Yan J, Kaufer D and Wu G: Dynamic hyper-graph inference framework for computer-assisted diagnosis of neurodegenerative diseases. IEEE Trans Med Imaging 38: 608-616, 2018.
140. Castellano G, Esposito A, Lella E, Montanaro G and Vessio G: Automated detection of Alzheimer's disease: A multi-modal approach with 3D MRI and amyloid PET. Sci Rep 14: 5210, 2024.
141. Chatterjee I and Bansal V: LRE-MMF: A novel multi-modal fusion algorithm for detecting neurodegeneration in Parkinson's disease among the geriatric population. Exp Gerontol 197: 112585, 2024.
142. Chen H, Guo H, Xing L, Chen D, Yuan T, Zhang Y and Zhang X: Multimodal predictive classification of Alzheimer's disease based on Attention-combined fusion network: Integrated neuro-imaging modalities and medical examination data. IET Image Processing 17: 3153-3164, 2023.
143. Huang G, Li R, Bai Q and Alty J: Multimodal learning of clinically accessible tests to aid diagnosis of neurodegenerative disorders: A scoping review. Health Inf Sci Syst 11: 32, 2023.