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REVIEW ARTICLE

Artificial intelligence and biomarker approaches for Parkinson's disease detection

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Abstract

Parkinson's disease (PD) is a neurological syndrome or condition that occurs due to a deficit of dopamine-producing neurons in the substantia nigra. Diagnosing PD in its early stages is difficult, as its symptoms often resemble those of other neurological diseases. Therefore, recognizing reliable biomarkers is important for discriminating PD from related conditions, monitoring disease progression, and evaluating responses to therapeutic interventions. PD biomarkers are categorized into the following classes: clinical, neuroimaging, biochemical and proteomic, and genetic. Ongoing research aims to discover the most effective PD biomarkers that could help doctors identify PD risk and accelerate early diagnosis. Artificial intelligence (AI) methods, including deep learning and machine learning, have become increasingly significant in recent years due to their ability to evaluate and process large volumes of medical data with high accuracy. Furthermore, these methods have contributed significantly to the early diagnosis and effective treatment of various diseases, such as cancer and neurological conditions, such as Alzheimer's disease, PD, and multiple sclerosis. Given that PD affects a large population, the present study aims to review the applications of AI approaches in the early diagnosis of PD and the latest advancements in the field of PD biomarkers. Promising results have been obtained using various AI algorithms, which are helpful not only in identifying the PD stages but also in supporting early diagnosis. However, the implementation of these techniques in clinical practice faces challenges, including data quality and variability, model interpretability, and the need for interdisciplinary collaboration.

Keywords: Artificial intelligence; Parkinson's disease; Machine learning; Biomarkers; Deep learning

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1. Introduction

Neurodegenerative diseases (NDs) are progressive conditions that damage various parts of the human nervous system, primarily affecting the brain.[1] Alzheimer's disease (AD) and Parkinson's disease (PD) are prominent examples of NDs. While many symptoms of these diseases are treatable, a definitive cure remains elusive, emphasizing the urgent need for more effective treatments and early interventions.

Diagnosing NDs in their early stages is crucial; failure to do so can lead to severe outcomes, including death. To handle this growing crisis, it is vital to prioritize methods for both diagnosis and treatment.

Reliable biomarkers are urgently needed that can, first, identify NDs in their early stages and indicate susceptibility to these conditions. Second, these biomarkers could assist in clinical diagnosis and help define the severity of the disease.

PD is rapidly increasing, damaging the health of millions of people worldwide. According to the World Health Organization,[2] the prevalence of PD has doubled over the past 25 years, with global assessments in 2019 indicating that more than 8.5 million people were suffering from the condition. The rates of disability and death associated with PD are rising faster than those for any other ND. In 2019, PD caused around 329,000 deaths, more than twice the number recorded in 2000.

Statistics[3] show that in the United States of America (USA), approximately one million people are affected by PD, with projections indicating that this figure will rise to 1.2 million by 2030. A similar trend is expected in countries, such as India. The rapid increase in PD cases presents significant economic challenges, placing a burden on both the economy and healthcare systems. In addition, PD creates social obstacles within communities.[4] Given the profound economic, social, and personal impacts of PD, it is crucial to optimize strategies for controlling this disease, particularly through early diagnosis.

As noted earlier, biomarkers are essential for diagnosing NDs and can facilitate the early diagnosis of PD. Artificial intelligence (AI), machine learning (ML), and deep learning (DL) methods have seen significant advancements over the past decade. This study provides insights into research linking various types of biomarkers with AI, ML, and DL methods for PD diagnosis. Given that AI encompasses both ML and DL approaches, the term AI is used broadly in the remainder of this study.

1.1. Motivation factors and research challenges

Clinicians face several challenges when diagnosing and treating PD, mainly related to precision, cost, and delays.

(i) Precision: identifying the complex clinical signs of PD, especially in its early stages, is challenging due to the similarity between PD and AD symptoms. This makes it difficult for doctors to differentiate between these two NDs. By the time PD is accurately diagnosed, it may be too late to implement effective control measures
(ii) Delays: diagnosing PD is a lengthy process, involving multiple steps from data gathering to analysis. The time gap between data collection and interpretation leads to delays in reaching a diagnosis and initiating treatment
(iii) Cost: the high costs associated with diagnostic and treatment procedures can restrict access to healthcare facilities, especially for those in need of early intervention.

Continuous innovation and the development of more efficient methods are important to overcome these challenges, achieving precise results at a lower cost and in a timely manner. The literature highlights the significant potential of AI techniques in addressing these issues. AI methods can quickly process and analyze data, reducing diagnostic delays and enabling early-stage treatment. In addition, AI reduces the need for manual intervention, thereby increasing diagnostic efficiency and lowering overall treatment costs.

1.2. Contribution

To the authors' knowledge, this study is the first comprehensive review of AI applications using four major types of biomarkers—clinical, neuroimaging, biochemical and proteomic, and genetic—for the early diagnosis of PD.

The key contributions of this review include:

(i) Systematically exploring the practicalities of AI approaches to enhance the efficiency and precision of PD diagnosis, management, and treatment
(ii) Analyzing the AI methods and techniques used in diagnosing and treating PD
(iii) Stratifying different biomarkers based on the available AI approaches.

1.3. Organization of the review

The organization of the remainder of the review is as follows: Section 2 discusses the background and various aspects of PD, along with relevant biomarkers and AI approaches. Section 3 elaborates on the research methodology used in this study, followed by findings from the literature related to the application of AI approaches in diagnosing, treating, and managing PD using different types of biomarkers. Section 4 discusses the challenges and future directions for applying AI in the medical field. Section 5 summarizes the review findings.

2. Background

2.1. PD process

PD is triggered by the degeneration of midbrain dopaminergic neurons (mDANs), which are crucial for controlling movement.[5] PD symptoms are categorized as motor and non-motor, and they develop gradually and worsen with age, significantly impacting the quality of life.[6] As PD progresses, it results in mental, physical, social, and emotional challenges. Early and accurate diagnosis is crucial before these symptoms become more severe. Other causes of PD include genetic and environmental factors,[7] as well as the presence of Lewy bodies.[8]

2.2. PD treatment

PD is a heterogeneous disorder that affects individuals' quality of life. While there is no curative therapy for PD, treatments are available. These treatments focus on improving the patient's quality of life and managing symptoms. Available options for treatment include[8] surgeries, therapies, medications, lifestyle adjustments, and supportive care.

Each PD patient is treated according to the severity of their condition, which is classified into five stages (Stage 1 to Stage 5). Treatment plans are tailored to the individual's specific needs and disease progression. Ongoing research is exploring new therapies, such as stem cell treatments and gene therapy, to improve outcomes and slow disease progression.[8] Recent advancements in PD treatment focus on improving symptom management, developing disease-modifying therapies, and incorporating new technologies based on AI methods. AI can use patient data (e.g., genetics, lifestyle, disease severity) to recommend personalized therapies, improving treatment efficacy and reducing medication side effects.

Another increasingly recognized class of PD biomarkers is known as "gut biomarkers." Although gut biomarkers span traditional biomarker categories, such as biochemical, genetic, microbiome, metabolomic, and even clinical and imaging domains, their focus on the gastrointestinal system and the gut-brain axis makes them a distinct subclass with unique diagnostic and pathogenic significance.

2.3. Biomarkers

According to the U.S. Food and Drug Administration and the National Institutes of Health,[21] "A biomarker is not intended to measure how an individual feels, functions, or survives. Instead, it is a defined characteristic that serves as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions." Different researchers have classified biomarkers into various categories. Some studies[22] have focused on clinical, biochemical, and neuroimaging biomarkers, while Surguchov[23] identified clinical, imaging, pathological, biochemical, and genetic markers as potential PD biomarkers. After reviewing the literature, we identified four major categories: clinical, neuroimaging, biochemical and proteomic, and genetic biomarkers. A summary of these categories is provided in Table 1.

Research on PD biomarkers is rapidly evolving, with significant advancements in areas, such as genetics, proteomics, neuroimaging, gut microbiome (GM),[24] and exosomal analysis.[16] The integration of AI methods with biomarkers offers greater precision in tracking PD progression and identifying novel targets for early intervention. In the following section, we explore research that utilizes various biomarkers in conjunction with AI-based techniques.

2.4. Integration of AI approaches

ML is a branch of AI focused on statistical models and algorithms that can make computers to enhance their performance on a task by learning from data. DL, a specialized subset of ML, uses artificial neural networks (ANNs) with multiple layers (hence "deep") to analyze various forms of data.[25] DL algorithms are robust and efficient, and are hence employed in medical imaging to address diagnostic issues.[26]

3. Related work

This section reviews selected research articles that focus on the application of AI in the diagnosis, management,

Table 1. Parkinson's disease biomarkers and their description

Type of biomarker	Description
Clinical[9-12]	These biomarkers are related to clinical signs and symptoms that aid in diagnosis and tracking disease progression. Non-motor signs include cognitive decline, sleep disturbances, fatigue, excessive sweating, depression, idiopathic rapid eye movement sleep-behavior disorder, and constipation. Motor signs include tremors, rigidity, akinesia, and postural instability, as well as two motor subtypes: postural instability, gait difficulty, and axial symptoms. Bradykinesia and stiffness exhibit the strongest correlation with the degeneration of dopamine-producing neurons in the nigrostriatal system
Neuroimaging[13,14]	These biomarkers use imaging techniques, such as MRI, SPECT, and PET to detect structural and functional changes in the brain, particularly in regions, such as the substantia nigra and dopamine transporter systems
Biochemical[15-17] and proteomic[16,18,19]	Biochemical biomarkers encompass a wide range of molecules and processes, such as proteins, metabolites, and cellular changes. Proteomic biomarkers focus specifically on proteins involved in the disease process. These biomarkers are found in cerebrospinal fluid, blood, and saliva. α-syn, dopamine metabolites (HVA, DOPAC), and neuroinflammatory markers are among the most studied
Genetic[16,20]	Genetic biomarkers are relevant to both familial and sporadic forms of PD. Mutations in genes, such as *PRKN*, *LRRK2*, and *GBA* are recognized as significant genetic contributors to the disease

Abbreviations: DOPAC: 3,4-dihydroxyphenylacetic acid; HVA: Homovanillic acid; MRI: Magnetic resonance imaging; PET: Positron emission tomography; SPECT: Single-photon emission computerized tomography; α-syn: α-synuclein.

and treatment of PD. The aim is to provide an overview of recent advancements and practical implementations of AI methods within the field. The articles are analyzed based on the methodologies employed and the results obtained across various biomarker types. This structured comparison allows readers to gain a deeper comprehension of how AI techniques and biomarkers are being integrated in efforts to diagnose, manage, and treat PD effectively.

3.1. Methodology

This review aims to examine AI-based approaches for evaluating different types of biomarkers and to provide a comprehensive understanding of their role in PD diagnosis. The research questions guiding this study are presented in Table 2. To conduct this review, we identified, filtered, and assessed relevant research from recent years, focusing on the utilization of AI approaches in diagnosing, managing, and personalizing PD treatment using various types of biomarkers.

3.2. Application of AI methods for PD: an overview

The use of AI approaches has considerably improved the accuracy and speed of PD identification and management. These methods can rapidly and precisely analyze large volumes of medical data, including diverse biomarkers, such as brain images and clinical information, by identifying complex patterns that assist in early PD diagnosis.[26] In addition, AI methods are effective in predicting patients' responses to different types of treatments, such as deep brain stimulation.[27] Predictive disease progression algorithms can also aid in developing personalized treatment plans. In addition, by modeling the effects of new treatments and refining treatment protocols, these approaches can expedite the development of new drugs and therapeutic strategies, thereby enhancing their effectiveness.[26] In this section, we assess the applicability of AI methods to PD-related studies that utilize various types of biomarkers.

3.2.1. Clinical biomarkers and AI methods

Clinical biomarkers encompass both motor and non-motor features of PD.[22] Clinical rating scales are utilized to identify these features and assist in early diagnosis. Some commonly used scales include the Hoehn and Yahr scale (H&Y), the Non-Motor Symptoms Scale for PD, and the Unified PD Rating Scale (UPDRS).[22]

As previously mentioned, AI methods are crucial for PD diagnosis. In this section, we explore research that integrates various clinical biomarkers alongside AI-based techniques for the detection, monitoring, and classification of PD patients from healthy individuals.

An automated approach based on a DL method was proposed for PD detection and severity prediction by analyzing gait data.[28] The study involved 166 participants, including 93 PD patients and 73 control subjects. That method achieved 98.7% accuracy for PD gait recognition and 85.3% for predicting PD severity.

Goyal and Rani[29] conducted a comparative analysis of ML, ensemble learning (EL), and DL classifiers to develop classification models for PD detection using 252 voice samples (188 PD and 64 healthy). The random forest (RF) model, with 82.37% accuracy, gave better performance than other base classifiers. The DL model achieved training

Table 2. Research questions

Item	Question	Description
1	What types of biomarkers are used by researchers to diagnose, monitor, and treat PD?	This question aims to identify the categories of biomarkers used in the diagnosis, monitoring, and treatment of PD
2	Which AI methods are used to classify PD subjects from healthy subjects?	This question explores which methods—AI, ML, or DL—are employed by researchers to distinguish PD subjects from healthy individuals
3	What performance parameters are reported in the research manuscripts?	This question seeks to identify the performance metrics used to evaluate the effectiveness of AI methods in classifying and diagnosing PD subjects compared to healthy individuals
4	How do AI methods offer new insights into the PD diagnosis and treatment process?	This question investigates how AI methods contribute to new insights in the diagnosis and treatment of PD. Due to their data-driven nature, these approaches can significantly improve early detection, monitoring, and personalizing treatment
5	What strategies can be recommended to improve the efficiency and effectiveness of these approaches in diagnosing and treating PD?	This question aims to identify practical strategies to enhance the performance and impact of AI methods in PD diagnosis and treatment
6	How many subjects were evaluated in each study?	This question examines the sample size in each study, as the performance of AI methods can vary based on dataset size. Understanding the number of subjects helps assess the context and reliability of the model's performance

Abbreviation: AI: Artificial intelligence; DL: Deep learning; ML: Machine learning; PD: Parkinson's disease.

and testing accuracies of 91.33% and 85.02%, respectively, showing comparable performance to traditional ML classifiers, despite the small dataset. Among EL classifiers, the Light Gradient Boosting Machine model showed the highest accuracy (85.90%), outperforming both ensemble and base models.

Senturk[30] employed ML algorithms to detect PD using voice features from 31 subjects (23 PD and eight healthy). Using support vector machines (SVM) with the recursive feature elimination (RFE) algorithm, the study achieved a diagnostic accuracy of 93.84% with a minimal number of voice features.

Ouhmida *et al.*[31] proposed an approach for PD detection using voice features and ML algorithms on Max Little's University of California, Irvine (UCI) dataset, consisting of 195 samples from 31 subjects (23 PD and eight healthy). The study applied K-nearest neighbors (KNN), SVM, and decision tree (DT) classifiers, combined with two feature subset selection (FSS) techniques: Minimum Redundancy Maximum Relevance (mRMR) and ReliefF. The KNN algorithm outperformed the other, achieving 98.26% area under the curve (AUC), 97.22% sensitivity, 100% specificity, and 97.92% accuracy.

Chintalapudi *et al.*[32] highlighted the contribution of ML methods to improving disease prediction accuracy. Using voice data from 31 subjects (23 PD and eight healthy) in the UCI dataset, they tested three DL models—recurrent neural networks (RNN), multilayer perceptron (MLP), and long short-term memory (LSTM). The LSTM model outperformed the others, achieving 99% accuracy.

Ferreira *et al.*[33] applied the Naïve Bayes (NB) algorithm to spatiotemporal gait parameters collected from 126 participants (63 idiopathic PD [iPD] and 63 healthy), achieving 84.6% classification accuracy, 80.0% recall, and 92.3% precision. For PD stage identification, the RF model yielded an AUC-receiver operating curve (ROC) of 78.6%.

Sigcha *et al.*[34] employed consumer smartwatches equipped with inertial sensors and ML methods to detect and assess bradykinesia in the upper limbs. Thirteen participants (six PD and seven age-matched controls [AMC]) wore smartwatches while performing motor tasks over a minimum period of 6 weeks. A combination of convolution neural networks (CNN) and RF models produced promising results, achieving 86% accuracy and 94% AUC. This approach offers an unobtrusive and effective method for detecting and evaluating the severity of bradykinesia.

Thakur *et al.*[35] implemented and compared ML algorithms for PD diagnosis using a voice dataset consisting of 252 subjects (188 PD [107 males and 81 females] and 64 healthy [23 males and 41 females]), with 756 instances and 754 features, sourced from www.kaggle.com. The authors utilized SVM, RF, DT, and extra trees (ET) classifiers for PD diagnosis. The best performance was achieved using the ET classifier, with an accuracy of 94.34%, precision of 93.88%, F1-score of 96.84%, and a recall of 100%.

Trabassi *et al.*[36] identified the most accurate supervised ML algorithm for classifying PD subjects from speed-matched healthy individuals using a minimal set of gait features derived from inertial measurement units. Data from 161 subjects (81 PD and 80 healthy) included 22 gait features extracted from trunk acceleration patterns. After applying a three-level FSS, seven gait features were utilized to execute five ML algorithms - DT, SVM, KNN, ANN, and RF. Among these, on test dataset, DT, SVM, and RF shown the highest prediction accuracies exceeding 80%.

Alalayah *et al.*[37] used a dataset comprising 195 voice signals (48 healthy and 147 PD) and applied ML classification algorithms for early PD detection. Their method (RF with t-distributed stochastic neighbor embedding) outperformed existing studies, achieving 97% accuracy, 96.50% precision, 94% recall, and 95% F1-score. In addition, the MLP and principal component analysis (PCA) algorithm achieved 98% accuracy, 97.66% precision, 96% recall, and 96.66% F1-score.

Govindu and Palwe[38] employed four ML methods for the early detection of PD based on voice data from 31 subjects. They found that the RF classifier provided the best PD classification results, with 91.83% accuracy, 95% sensitivity, 86% recall, and an ROC-AUC of 70.1%, using the Multidimensional Voice Program dataset consisting of 195 records with 22 features.

Martinez-Eguiluz *et al.*[39] evaluated nine ML algorithms to differentiate PD subjects from controls using non-motor attributes. The data were sourced from the Biocruces database (96 subjects: 59 PD and 37 healthy) and the Parkinson's Progression Markers Initiative (PPMI) (687 subjects: 490 PD and 197 healthy). Most ML algorithms achieved accuracy exceeding 80%, with SVM and MLP performing best, at 86.3% and 84.7% accuracy, respectively.

Yadav *et al.*[40] introduced an approach to assess the stage and severity of PD using a voice dataset comprising 31 subjects (23 PD and eight healthy), 23 features, and 197 instances, leveraging AI algorithms. The study indicated that the DT classifier achieved 94.87% accuracy and gradient boosting classifier has an AUC of 98.7%.

Goyal *et al.*[41] proposed a Repetitive Pointing Task to evaluate upper-limb bradykinesia utilizing data collected through a 3D motion capture system for nine healthy and 17 PD subjects. Using just six features, their proposed ML

model achieved 97.14% accuracy, 97% sensitivity, 95% specificity, 97% precision, and a 97% F1-score. The authors emphasized that their method is a fast, reliable, and non-invasive method for assessing bradykinesia and estimating PD stages.

Faiem *et al.*[42] used a gait dataset from the "PhysioNet" repository, consisting of 93 PD and 73 control subjects, and implemented a perceiver-based multimodal ML framework to predict UPDRS scores for PD patients. Their model achieved a root mean square error of 5.75 ± 4.16, a mean absolute error (MAE) of 2.23 ± 1.31, and a linear correlation coefficient (CC) of 0.93 ± 0.08. These values are better than previous studies in both MAE and CC, highlighting the effectiveness of their multimodal approach.

Palakayala and Kuppusamy[43] demonstrated that PD can be identified with high precision by analyzing non-motor PD features using ML algorithms. To support this, they collected data from 212 participants (106 healthy and 106 PD), who underwent the PD Sleep Test, the Hopkin's Verbal Learning Test, and the Clock Drawing Test from the PPMI database. The study showed that all applied ML classification algorithms—RF, NB, SVM, and logistic regression (LR)—achieved accuracies exceeding 73% ± 8.4% with individual datasets, while an accuracy of 98% ± 0.6% was achieved using a custom hybrid dataset.

Salsone *et al.*[44] investigated the performance of ML models—LR, SVM, RF, and extreme gradient boosting (XGB)—to classify idiopathic REM sleep-behavior disorder (iRBD) patients who exhibited periodic leg movements (PLMS) from those who did not. The study utilized heart rate variability data from 42 consecutive iRBD subjects (19 without PLMS and 23 with PLMS). Their findings demonstrated that the RF model achieved 86% accuracy, 74% specificity, and 96% sensitivity. XGB (accuracy = 78%, specificity = 72%, sensitivity = 83%) and SVM (accuracy = 81%, sensitivity = 83%, specificity = 79%) also performed well. LR exhibited the lowest performance with 71% accuracy.

Wang *et al.*[45] introduced a hybrid signal processing and ML-based gait classification system to detect gait anomalies and assess PD severity levels. Five different ML classifiers were employed for anomaly detection and severity rating as defined in H&Y scale. To verify the system's effectiveness, the "Physionet" gait database, comprising data from 93 individuals with iPD and 73 AMCs, was utilized. Employing a 10-fold cross-validation method, the SVM classifier achieved the highest accuracy, reporting 98.20% for anomaly detection and 96.69% for severity level assessment.

Byeon[46] developed an SVM-based framework to predict depression in PD (DPD) using National Parkinson's Registry data from 223 subjects (130 without depression and 93 with DPD) out of a total of 335. The model incorporated predictors, such as health habits, PD symptoms, sociodemographic factors, sleep behavior syndromes, and neuropsychological indicators. Comparing the prediction accuracy of eight different SVM models, the study found that Gaussian Kernel-based Nu-SVM achieved the highest performance, with 96.0% sensitivity, 93.3% specificity, and 95% overall accuracy. In contrast, the polynomial-based C-SVM reached the maximum sensitivity (100%) but had the least specificity (20%) and an overall average accuracy of 70%.

Lee and Ham[47] conducted a review of ML advancements for early depression diagnosis, analyzing 32 original studies out of 120 identified in the Web of Science. They highlighted that various ML methods are suited to different data types. For instance, LR, RF, SVM, and ANN are effective for numeric data, while RF is particularly suitable for genomic data. The reported performance metrics varied widely, with accuracy scores ranging from 60.1% to 100.0% and AUC scores from 64.0% to 96.0%. The study concluded that ML is a valuable tool for the early diagnosis of depression.

Pereira *et al.*[48] explored the relationship between gut bacteria, serum metabolites, and clinical features in 124 subjects (63 PD and 61 healthy). They identified 139 metabolite features that distinguished PD from healthy subjects; however, no associations were found between clinical features within the PD group and metabolic attributes. Using SVM with a radial basis function kernel, they achieved 81% accuracy with gas chromatography-mass spectrometry (GC-MS) data and 72% and 77% accuracy with liquid chromatography-mass spectrometry (LC-MS) in negative and positive ionization modes, respectively.

Li *et al.*[49] presented an AI-based approach for assessing PD grades, aiming to improve standardization and accuracy, avoiding the challenges related to wearable sensors. A dataset of 110 videos was collected from various people with different PD severity levels. Employing MediaPipe, 19 distinct kinematic features were extracted from joint movements, generating real-time kinematic data. Among five different ML algorithms (SVM, Gradient Boosting DTs, KNN, MLP, and RF) tested, KNN delivered the highest overall accuracy of 96.63% and achieved 100% accuracy in distinguishing PD grade 4 from grade 5 subjects.

Lu *et al.*[50] presented a method for extracting time-frequency-based statistical features from dynamic handwriting patterns, focusing on their temporal and frequency characteristics for PD detection. This approach

was evaluated using the Cc-PhD dataset (97 subjects: 31 PD, 31 Essential Tremor, and 35 healthy) and the Parkinson's Disease Handwriting Database (PaHaW) dataset (75 subjects: 37 PD and 38 healthy). An Escape Coati Optimization Algorithm was applied to optimize the parameters of the AdaBoost classifier after FSS was performed using the RF algorithm. The method achieved 97.95% and 98.67% accuracy; 98.15% (average) and 97.78% sensitivity; 99.17% (average) and 100% specificity; and AUC scores 98.66% (average) and 98.89% on the Cc-PhD and PaHaW datasets, respectively.

These findings collectively demonstrate that AI methods can effectively utilize clinical biomarkers to accurately differentiate PD subjects from healthy individuals. The results highlight the potential of such methods to serve as valuable tools in clinical settings, supporting early diagnosis, continuous monitoring, and personalized treatment strategies for PD patients.

3.2.2. Neuroimaging biomarkers and AI methods

In this section, we explore the research conducted so far that utilizes various neuroimaging biomarkers alongside AI methods for detecting, monitoring, and classifying PD subjects from healthy individuals.

Castillo-Barnes *et al.*[51] used ML methods to classify PD and healthy subjects using a balanced set of 386 single-photon emission computerized tomography (SPECT) scans, from 386 subjects (193 PD [127 males and 66 females] and 193 healthy [128 males and 65 females]), from the PPMI. FSS was performed using a Mann-Whitney-Wilcoxon U-test, and classification was carried out using an SVM approach. The authors achieved a balanced accuracy of 97.04% using 10-fold cross-validation, demonstrating the efficacy of the SVM-based framework for distinguishing PD subjects from controls.

Chakraborty *et al.*[52] applied four ML algorithms for the detection of PD based on 3T T1- magnetic resonance imaging (MRI) scans from 906 subjects (203 control, 66 prodromal, and 637 PD). They reported 95.3% accuracy, 97.28% precision, 95.41% recall, and a 94% F1-score using an ANN (specifically an MLP) for PD detection.

In a separate study, Chakraborty *et al.*[53] applied a 3D CNN for PD detection on 3T T1w-MRI scans from 406 subjects (203 PD and 203 healthy) and achieved 95.29% accuracy, 94.3% average recall, 92.7% average precision, 94.30% average specificity, a 93.6% F1-score, and 98% ROC-AUC.

Huang *et al.*[54] evaluated a dataset of functional brain images from 202 subjects (six healthy and 196 PD). They applied various prediction approaches, including multivariate statistical analysis, EL models, and deep CNNs, to predict PD stages. The VGG16 deep CNN model achieved 92.2% training accuracy, 64.9% test accuracy, and 57.6% test F1-score.

Magesh *et al.*[55] employed ML methods for early PD diagnosis using 642 (430 PD and 212 non-PD) SPECT dopamine transporter scans from the PPMI. Using a VGG16 deep CNN, they achieved 95.2% accuracy, 97.5% sensitivity, and 90.9% specificity for classifying PD and non-PD subjects.

Solana-Lavalle and Rosas-Romero[56] conducted MRI-based PD detection by using voxel-based morphometry and seven ML classifiers on a dataset of 480 MRI images (226 PD males, 86 healthy males, 104 PD females, and 64 healthy females) from the PPMI. In male subjects, the NB classifier with 1.5T scanner achieved 99.01% accuracy, 100% precision, 100% specificity, while SVM with 3T scanner achieved 99.35% sensitivity. For female subjects, the logistic classifier with 1.5T scanner achieved 96.97% accuracy, 97.22% precision, and 96.15% specificity, Bayesian network with 1.5T scanner achieved 100% sensitivity, while MLP with 1.5T scanner achieved 96.15% specificity. These results highlight the effectiveness of ML algorithms in detecting PD across genders.

Shu *et al.*[57] examined 144 subjects (72 subjects with PD progression and 72 with stable PD) for predicting disease progression using T1-weighted MRI scans and ML. Their proposed joint model achieved an AUC of 83.6%, compared to 79.5% and 55.0% for the radiomics signature and UPDRS score, respectively. Sensitivity values of 80.5%, 87.5%, and 29.2%, and specificity values of 72.2%, 69.7%, and 86.1% were also reported. For Stage 1 PD, the model achieved 82.7% predictive accuracy, 82.9% sensitivity, and 70.2% specificity; for Stage 2, it achieved 85.4% accuracy, 96.0% sensitivity, and 60.0% specificity.

Veetil *et al.*[58] analyzed 242 MRI samples (150 PD and 92 normal control [NC] subjects) to classify PD and NC subjects using five deep neural network architectures: Xception, DenseNet201, VGG16, VGG19, and ResNet50. The highest accuracy of 92.60% was achieved using VGG19, along with an F1-score of 92.3% for NC and 92.9% for PD. The authors emphasized that AI-based tools are highly effective in supporting early risk assessments and serving as decision-support systems in PD medical imaging.

Guo *et al.*[59] classified early-stage PD using resting-state functional MRI (rs-fMRI) data from 84 subjects (28 in Stage 1 and 56 in Stage 2) from the PPMI. The LSTM model achieved an accuracy of 71.63%, which was 11.56% higher than the CNN and 13.52% higher than the best-performing traditional ML model. These results demonstrated a considerable enhancement in accuracy

and robustness compared to other ML classifiers.

Tomer *et al.*[60] compared ML methods for PD detection using T1-weighted MRI scans from 20 individuals, including both PD and NC groups. Of the 968 pre-processed images, only 848 were used for analysis. For feature extraction, the gray level co-occurrence matrix (GLCM) method achieved 90.5% accuracy, surpassing PCA, which yielded 87.5% accuracy.

Vyas *et al.*[61] used 318 brain images from MRI scans and applied both 2D and 3D CNN models for PD early detection. The 3D CNN model demonstrated 88.9% accuracy with an AUC of 86% on the test data, whereas the 2D CNN model showed 72.22% accuracy with an AUC of 50%.

Camacho *et al.*[62] trained a 3D CNN model to detect PD using 2041 T1-weighted MRI scans (1024 PD and 1017 healthy) collected from 13 different studies. Their model achieved 79.3% accuracy, 77.7% sensitivity, 81.3% specificity, 80.2% precision, and an AUC-ROC of 87%.

Erdaş and Sümer[63] developed a fully automated approach utilizing 1130 T1-weighted MRI scans (259 healthy and 871 PD) for detecting and predicting PD severity. Their method employed DL techniques, specifically 2D and 3D CNNs. The 3D CNN model achieved 96.20% accuracy, 95.36% recall, 94.52% F1-score, and 94.07% precision.

Khachnaoui *et al.*[64] proposed a computer-aided diagnosis system for PD using pre-trained CNN models, the bilinear pooling method, and the transfer learning (TL) technique, based on 2720 SPECT images (1360 PD and 1360 healthy) from the PPMI. An accuracy of 98.47% was achieved by using the Bilinear CNN EfficientNet-B0-MobileNet-V2 model. The authors concluded that their method supports accurate PD diagnosis without relying on subjective factors.

Wang *et al.*[65] employed a DL model to analyze quantitative susceptibility maps and T1-weighted images for distinguishing PD patients from healthy subjects. They used two datasets: Dataset 1 with 379 subjects (92 PD and 287 healthy), and Dataset 2 with 155 subjects (83 PD and 72 healthy). In the internal testing sample, the model achieved an AUC of 90.1%, 92.0% accuracy, 83.3% sensitivity, and 94.7% specificity. In the external testing sample, it achieved 84.5% AUC, 78.7% accuracy, 77.1% sensitivity, and 80.6% specificity.

Praneeth *et al.*[66] proposed a technique for classifying PD by using a deep residual CNN combined with the Enhanced Whale Optimization Algorithm to improve classification accuracy. Using 591 diffusion-weighted and T1-weighted MRI scans from the PPMI (412 PD and 179 healthy), they achieved 98.87% accuracy, 97.02% precision, 96.87% sensitivity, and 98.13% specificity in distinguishing PD from healthy subjects.

Ahalya *et al.*[67] proposed an automated PD detection method based on CNN and quantum SVM, using 1000 MRI images, including 60 real-time MRIs (30 healthy and 30 PD). Their hybrid model achieved 87.5% prediction accuracy, 84% recall, 95% precision, and an F1-score of 89%.

Islam *et al.*[68] aimed to analyze PD by applying ML and TL techniques to clinical assessment data and 3D T1-weighted MRI samples. They used two datasets: 1277 clinical records (155 PD and 1122 healthy) and 2500 usable MRI samples (1236 PD and 1244 healthy) from the PPMI. Using the ET classifier, an accuracy of 98.44%, 97.11% precision, 99.02% recall, and a 98.06% F1-score, was attained. In addition, implementing DenseNet169 on the MRI dataset resulted in an optimal accuracy of 85.08%.

Patil and Ford[69] proposed a decorrelated CNN framework to recognize PD using rs-fMRI data. The proposed framework was applied to two datasets: a single-scanner PPMI imbalanced dataset (183 subjects: 164 PD and 19 healthy) and a multi-scanner dataset. After pre-processing, the multi-scanner dataset was formed by combining rs-fMRI data from 215 healthy subjects in the frontotemporal lobar degeneration neuroimaging initiative with those obtained from the PPMI. The model achieved 77.80% accuracy on the multi-scanner dataset, outperforming the single-scanner model.

Redhya and Jayalakshmi[70] proposed an ensembled grid based ML model, for MRI-based PD classification, using 260 MRI images (134 PD and 126 healthy) from the PPMI. The stacking classifier, which combines XGB, SVM, and RF classifiers, achieved 98.41% accuracy in distinguishing PD from healthy subjects.

Zhang *et al.*[71] analyzed T1-weighted MRI images and clinical data from 272 PD subjects in the PPMI, alongside 45 PD subjects from the National Alzheimer's Coordinating Center dataset, to identify depression subtypes in PD subjects using ML methods. By employing PCA and four other unsupervised clustering algorithms, they observed that "Partitioning Around Medoids" outperformed "Gaussian Mixture Model," hierarchical clustering, and K-means with two clusters. The sensitivity, specificity, and AUC in the high-risk testing subtype were 78.6%, 81.5%, and 81%, respectively. The model based on non-high-risk subtypes had an AUC of 85.9%, sensitivity of 65.4%, and specificity of 85.2%.

These findings collectively demonstrate that AI techniques can effectively leverage neuroimaging

biomarkers to distinguish PD from healthy subjects with high accuracy. The results from this research support the potential for such methods to become integral tools in clinical settings, aiding early diagnosis, continuous monitoring, and personalized care for individuals with PD.

3.2.3. Biochemical and proteomic biomarkers and AI methods

Biochemical biomarkers for PD comprise a broad category of markers that indicate the presence or progression of the disease. These biomarkers include various molecules, such as proteins, hormones, metabolites, lipids, and neurotransmitters. Proteomic biomarkers, a significant subset of biochemical biomarkers, refer specifically to proteins; however, the broader biochemical biomarker category includes other molecules that offer meaningful insights into the disease.[72]

Proteins, such as α-synuclein (α-syn), neurofilament light chain, and DJ-1 serve as markers of PD progression. These are analyzed using proteomic techniques, such as mass spectrometry and protein assays to understand their roles in the disease. α-syn is particularly crucial to PD pathology due to its misfolding and aggregation, which leads to the formation of Lewy bodies,[17] a hallmark of PD.[73]

It is important to note that while all proteomic biomarkers are biochemical, the reverse is not true. For example, neurotransmitters, such as dopamine metabolites are widely used as biochemical biomarkers in PD research, but they fall outside the scope of proteomics. These molecules are essential in understanding PD pathophysiology and are typically analyzed using techniques, such as liquid chromatography combined with tandem mass spectrometry.[16]

In this section, we examine research studies that have explored the use of biochemical and proteomic biomarkers, alongside AI methods, for detecting, monitoring, and classifying PD subjects from healthy individuals.

Lin *et al.*[74] developed ML algorithms utilizing blood-based biomarkers to identify subjects affected by AD, PD, and frontotemporal dementia (FTD). Plasma samples from 377 subjects were analyzed, including 97 healthy, 76 subjects on the AD spectrum (41 mild cognitive impairment [MCI] and 35 with AD), 173 on the PD spectrum (57 with normal cognition, 29 with MCI, and 87 with PD dementia), and 31 with FTD. Plasma levels of α-syn, amyloid beta (Aβ) 42, total tau, Aβ40, and phosphorylated Tau181 were measured. The developed linear discriminant analysis (LDA) model combined with a RF classifier achieved a 76% accuracy in distinguishing AD, PD, and FTD, and 63% and 83% accuracy in distinguishing disease severity in the PD and AD spectrums, respectively.

Maass *et al.*[75] validated a predictive SVM model for classifying PD and AMC based on cerebrospinal fluid (CSF) bioelement levels. The study included 157 subjects (82 PD, 68 AMC, and seven normal pressure hydrocephalus), achieving an AUC-ROC of 76%, sensitivity of 80%, and specificity of 83% on a new dataset, without incorporating additional features.

Wang *et al.*[76] introduced a DL technique to detect early PD by using pre-motor features, such as iRBD, CSF biomarkers, olfactory loss, and mDAN imaging markers. By comparing their DL model with 12 ML and EL methods on a dataset of 584 subjects (183 healthy and 401 early PD), they found that their framework achieved the highest average accuracy of 96.45%.

Chung *et al.*[77] examined the impact of plasma extracellular vesicles (EV)-borne tau and Aβ1-42 as biomarkers for cognitive deficit in PD, using a dataset of 162 subjects (46 healthy and 116 PD). Subjects were classified according to cognitive function. Using an ANN, their model achieved 91.3% accuracy in detecting cognitive dysfunction in PD patients. Aβ1-42 and plasma EV tau were found to be the most significant factors.

Vacchi *et al.*[78] developed a two-level RF model to distinguish PD from atypical parkinsonisms (AP) using CSF-derived EVs and immune profiling of plasma-derived EVs. The Level 1 "basic" model, applied to 84 subjects (29 PD, 36 healthy, nine multiple system atrophy, and 10 AP-TAU), achieved 92.9% accuracy, 100% sensitivity, and 83.3% specificity in classifying subjects with NDs from healthy individuals. The Level 2 "integrated" model, trained on 54 subjects (48 patients and six healthy), achieved 92.6% accuracy and 96.6% sensitivity in distinguishing PD from healthy subjects. The advanced RF model also performed better in distinguishing AP-Tau, achieving 92.6% accuracy and 70.0% sensitivity compared to the basic model.

Amboni *et al.*[79] aimed to identify important features related to PD with MCI (PD-MCI) using an ML approach. A total of 75 PD subjects (42 without PD-MCI and 33 with PD-MCI) were evaluated through neuropsychological and clinical assessments. Two ML-based models were created: Model 1 combined age, gait, and clinical features, while Model 2 had two variants—Model 2A and Model 2B. Model 2A used mean standardized uptake values of nine brain areas along with the top five features identified in Model 1. Model 2B focused on cortical regions combined with those same top five features. The best performing classifiers in Model 1 were SVM (accuracy = 80.0%, AUC-ROC = 79.2%, sensitivity = 72.7%, specificity = 85.7%) and RF (accuracy = 73.3%, AUC-ROC = 72.2%, sensitivity = 66.7%, specificity = 78.6%). In Model 2A, the

highest performer was SVM (accuracy = 72.2%, specificity = 70.6%, sensitivity = 73.7%, AUC-ROC = 72.1%) and in Model 2B, SVM (accuracy = 75.0%, sensitivity = 73.7%, specificity = 76.5%, AUC-ROC = 75.1%) outperformed other classification algorithms. Overall, Model 1 provided the highest accuracy, and SVM consistently outperformed other classifiers.

Chen *et al.*[80] developed a predictive model for assessing cognitive deterioration in 42 PD by using ML methods. For each participant, three plasma biomarkers and 29 clinical variables were collected, along with neuropsychological test results. ML techniques, including SVM and PCA, were employed to build a cognitive classification model. Using 32 predictive features, the PCA-SVM classifier achieved an accuracy of 92.3% and an AUC of 92.9%. When only 13 carefully selected features were used, the accuracy and AUC both increased to 100%.

Dadu *et al.*[81] applied supervised and unsupervised ML methods to comprehensive and longitudinal clinical data from the PPMI, which included 294 subjects, to predict PD progression and uncover distinct patient subtypes. An independent dataset consisting of 263 clinically well-characterized cases from the PPMI was used to validate the models. The authors made predictions of PD progression over 5 years following initial diagnosis, achieving average AUCs of 95% ± 2% for fast-progressors, 87% ± 3% for moderate progressors, and 92% for the slow progressors. They also recognized serum neurofilament light as a crucial biomarker for rapid PD progression, along with several other significant indicators of disease progression.

Harvey *et al.*[82] provided an approach to predict cognitive outcomes in newly diagnosed PD subjects, from the PPMI, by developing a multivariate ML model. The dataset included 67 with normal cognition, 39 with PD-MCI, 43 with PD dementia, and 60 with subjective cognitive decline. Four ML methods were evaluated: RF, conditional inference forest (Cforest), SVM, and ElasticNet. For the cognitive impairment model, the following results were obtained: the combined model (clinical and biological data) achieved 86.7% accuracy, 71.9% sensitivity, 93.8% AUC, and 96.1% specificity using Cforest (28 variables). The clinical features model using Cforest (11 variables) yielded 85.5% accuracy, 65.6% sensitivity, 93.0% AUC, and 98.0% specificity. The biofluid model using ElasticNet (four variables) achieved 68.7% accuracy, 62.5% sensitivity, 75.6% AUC, and 72.5% specificity. For PD dementia prediction, the combined model (clinical and biological data) using SVM (10 variables) achieved 81.9% accuracy, 47.1% sensitivity, 86.2% AUC, and 90.9% specificity. The clinical features model using RF (eight variables) achieved 80.7% accuracy, 47.1% sensitivity, 82.8% AUC, and 89.4% specificity. The biofluid model using ElasticNet (five variables) yielded 86.7% accuracy, 47.1% sensitivity, 83.5% AUC, and 97.0% specificity.

Pahuja and Prasad[83] applied DL architectures to detect PD by integrating biological, MRI, and SPECT features from 132 subjects (73 PD and 59 healthy) obtained from the PPMI. Using a CNN model, the highest accuracy achieved was 92.38% and 93.33% in the model-level and feature-level frameworks, respectively.

Yang *et al.*[84] developed an AI model for PD detection and monitoring its progression using nocturnal breathing signals. Evaluation of the model was performed on a dataset of 7671 subjects (757 PD and 6914 control) obtained from public cohorts as well as hospitals in the USA. The AI model achieved an AUC of 90% on held-out test sets and 85% on external test sets. It also demonstrated the ability to predict PD progression and severity, showing a strong correlation with the Movement Disorder Society (MDS)-UPDRS scores.

Allwright *et al.*[85] applied an integrated ML algorithm to the United Kingdom (UK) Biobank dataset and found that neutrophil-to-lymphocyte ratio and elevated serum insulin-like growth factor 1 levels may help predict PD risk. Their analysis of 1753 measured non-genetic variables included 334,062 eligible participants, among whom 2719 developed PD since enrollment. The findings support improved early PD diagnosis and potential therapeutic strategies.

Almgren *et al.*[86] developed and evaluated a multimodal ML model to predict cognitive decline in 213 PD patients from the PPMI. The model incorporated CSF, clinical test scores, brain volumes, and genetic variants. An iterative scheme combining the RReliefF-based feature ranking and support vector regression with 10-fold cross-validation was used to identify optimal predictive features and evaluate the performance of that model. A correlation of 0.44 was observed between actual and predicted Montreal Cognitive Assessment scores. The study also revealed that several predictive features of cognitive impairment in PD, such as tau pathology and CSF Aβ, are commonly associated with AD, suggesting an overlap in cognitive decline mechanisms between PD and AD.

Kelly *et al.*[87] applied five ML approaches—LR, RF, SVM, XGB, and MLP—to identify blood-based biomarkers for PD and AD, utilizing various feature selection methods. After pre-processing, the GSE99039 PD cohort was randomly divided into a training cohort of 303 subjects (162 controls and 141 PD) and a test cohort of 131 subjects (68 PD and 63 controls), initially including 20,183 features. For PD, the RF model achieved an ROC-AUC of 74.3% while the CNN model achieved 71.5%.

McFall *et al.*[88] identified multi-modal predictors in PD using RF classifier combined with an explainable AI (XAI) method (Tree SHapley Additive exPlanation [Tree SHAP]) and biomarkers from MRI, clinical, etc. They tested 38 predictors across 10 domains to differentiate PD without dementia (PDND) from incipient dementia (PDID). The RF model classified PDID from PDND with an AUC of 84% and a normalized Matthew's correlation coefficient (MCC) of 0.76. Tree SHAP revealed that 10 key features accounted for 62.5% of the model's performance, indicating that dementia risk arises from multiple domains.

Tsukita *et al.*[89] integrated high-throughput CSF proteomics and ML to identify CSF signatures associated with PD using data from 279 non-genetic PD subjects and 141 healthy controls from the PPMI. The Least Absolute Shrinkage and Selection Operator (LASSO) method selected 14 differentially expressed proteins from 23 candidates to construct the PD proteomic score (PD-ProS), which showed strong performance with an AUC of 83%. This was validated in an independent internal validation dataset of 71 non-genetic PD subjects and 35 healthy subjects, achieving an AUC of 81%. In addition, PD-ProS distinguished 258 genetic PD subjects from 365 genetic prodromal subjects and predicted cognitive and motor decline, regardless of genetic status, with significant associations with dementia and H&Y stage IV.

Chen *et al.*[90] noted that CSF biomarkers are more sensitive for identifying prodromal PD than MDS measures. ML algorithms were applied to analyze fingerprint response patterns, enabling both qualitative and quantitative estimation of proteins. The KNN regression algorithm was used to evaluate MDS scores, achieving a mean square error of 38.88.

Dennis and Strafella[91] found that integrating various biomarkers, including neuroimaging and biofluids, can enhance diagnostic accuracy and predict cognitive deterioration in PD, based on a review of 21 studies. Their analysis revealed that MRI and functional MRI achieved accuracy and AUC scores above 80%. In addition, tau and Aβ42 were found effective in identifying PD subjects, with AUC scores and accuracy exceeding 90%.

Hällqvist *et al.*[92] used mass spectrometry-based proteomic phenotyping to find out blood biomarkers that could help detect at-risk individuals to slow PD symptom progression. Blood samples were analyzed from 99 recently diagnosed motor PD subjects, premotor were analyzed with iRBD from two datasets (18 and 54 subjects, longitudinally), and 36 healthy controls. The developed ML model, by analyzing the expression levels of eight proteins, correctly identified all individuals with PD and classified 79% of premotor individuals up to seven years before motor symptoms appeared.

Some studies[15-17] did not employ ML techniques but emphasized the significance of biological biomarkers in investigating PD progression, monitoring, and diagnosis. These studies highlighted the potential of various biological biomarkers to deepen our understanding of PD and improve clinical judgment in managing the disease.

In recent years, research on proteomic and biological biomarkers in PD has expanded significantly, offering new tools for diagnosis, monitoring, and insight into the disease's underlying mechanisms. Moreover, AI methods continue to advance the field by providing powerful means to analyze large-scale datasets and discover novel biomarkers. The combination of these AI technologies have potential for performing early PD detection with higher accuracy. This could enable clinicians to develop customized treatment strategies aimed at slowing disease progression and improving patient outcomes. Future PD research will likely focus on combining biomarkers with ML to broaden our understanding and enhance disease management.

3.2.4. Genetic biomarkers and AI methods

Genetic biomarkers refer to specific genetic variations that can be associated with the presence, progression, or susceptibility to a disease. In PD, several genetic mutations have been identified that are linked to hereditary forms of the disease, as well as to some sporadic cases. Key genes associated with PD include *SNCA*, *LRRK2*, *PRKN*, *GBA*, *VPS35*,[20] and *PINK1*.[20,93]

Falchetti *et al.*[94] conducted a gene expression meta-analysis of blood transcriptomes from PD and healthy subjects to identify gene signature of PD. Microarray data from four independent cohorts, totaling 711 instances (323 healthy and 388 iPD), were used for analysis. Collinearity recognition algorithms and RFE were employed to derive a 59-gene signature of iPD from the top 100 genes having the highest negative and positive effect sizes. Four sample size-adjusted training sets and nine classification algorithms are used to evaluate this gene signature. Of the 36 models created, 33 demonstrated accuracy greater than the non-information rate. Two models, based on SVM regression, exhibited the highest accuracy in predicting PD and healthy control samples.

Su *et al.*[95] provided valuable insights into the application of ML models by analyzing PD genetic and transcriptomic data. They reviewed studies and emphasized the significant potential of ML in revealing hidden patterns in PD transcriptomic and genetic data. Their review emphasized that the examined studies have successfully

uncovered important knowledge about the pathology and pathogenesis of PD, demonstrating the power of ML in advancing the understanding of the disease.

García-Fonseca *et al.*[96] suggested that ML is an important tool for classifying expression profiles of non-coding RNAs between healthy and PD subjects. Furthermore, these authors explained the importance of ML models in diagnosing NDs by summarizing results from various studies, which demonstrated accuracies ranging from 85% to 95% in ND detection using ML.

Hu *et al.*[97] conducted differential expression analysis (DEA) to identify differentially expressed genes (DEGs) deregulated in both PD and periodontitis using Gene Expression Omnibus (GEO) datasets. Genes associated with inflammatory response were retrieved from the Molecular Signatures Database. K-means clustering was employed for sample clustering, and LASSO model was used to perform FSS. Five genes—*PLAUR, TCIRG1, MANSC1, FMNL1*, and *RNASE6* —were determined as crosstalk biomarkers connecting periodontitis with PD.

Lam *et al.*[98] analyzed data from 1223 UK Biobank subjects to identify clinical and genetic biomarkers associated with NDs, namely, PD, AD, myasthenia gravis, and motor neuron disease. By employing an ML approach with Monte Carlo randomization, they identified biomarkers for predicting these NDs. The study demonstrated that, by training on available clinical markers, the multinomial model predicts NDs with an accuracy of 88.3%.

Makarious *et al.*[99] developed a model using GenoML on multimodal data from the PPMI to predict PD risk. These authors observed that when their final multimodal model was tested on males (65.57% PD and 63.74% control), it achieved 85.56% accuracy and 82.41% balanced accuracy, with 89.31% sensitivity and 75.51% specificity, outperforming the single modality data model. When validated on the PDBP dataset (males: 64.18% PD and 45.25% control), the tuned multimodal model achieved an AUC of 85.03%, with 43.07% specificity and 93.12% sensitivity.

Pantaleo *et al.*[100] used a robust ML approach to classify PD from healthy subjects in 579 samples collected from 390 individuals in the early PD group and 189 AMC individuals in the healthy group, using whole-blood transcriptomics data from the PPMI. Using a nested FSS method based on RF and XGB, they achieved an AUC of 72%. They also discussed the significance of the 493 candidate genes by using functional analysis based on Kyoto Encyclopedia of Genes and Genomes pathways and Gene Ontologies.

Vuidel *et al.*[101] differentiated the following into mDANs: induced pluripotent stem cells (iPSCs) derived from patients with the *LRRK2* G2019S mutation, an isogenic control, and iPSCs that are genetically not related. The authors identified increased levels of serine 129 phosphorylation and α-syn, decreased dendritic complexity, and mitochondrial dysfunction using automated fluorescence microscopy in a 384-well-plate format. ML methods were utilized to classify mDANs based on genotype and to identify drug-treated neurons using image-extracted features. The Z-factor (0.43) of SVM outperformed the Z-factor (0.12) of LDA. Their approach enhanced the applicability of mDANs in PD modeling and in identifying new LRRK2-linked drug targets.

Cai *et al.*[102] utilized SVM and weighted gene co-expression network analysis (WGCNA) for the identification of gene modules and the development of a PD diagnostic model using three GEO datasets. Sixty percent of the combined dataset (38 PD and 29 controls) was used for training, and 40% for testing, along with an external validation dataset (16 PD and nine controls). The developed model showed an AUC above 80% across the training, test, and validation sets, with performance confirmed through Synthetic Minority Over-Sampling Technique analysis. An AUC score of 74% for age features further validated the SVM model's reliability. These results suggest that combining WGCNA with SVM holds promise for biomarker screening and diagnostic model development for PD.

Hajianfar *et al.*[103] aimed to identify two gene mutations in PD by utilizing hybrid ML systems (HMLSs) based on non-imaging and imaging data. From the PPMI, 264 and 129 subjects with identified *LRRK2* and *GBA* mutation status were considered. Each dataset contained 513 features. Multiple HMLSs, consisting of 11 feature extraction or 10 FSS algorithms combined with 21 classifiers, were applied. In addition, Ensemble Voting was used for gene classification. For *LRRK2* and *GBA* mutation status prediction, several HMLSs achieved 98% ± 2% accuracy and 90% ± 8% accuracy, respectively, in five-fold cross-validation data. Additionally, 100% accuracy and 96% accuracy, respectively, were observed in external test data.

Wang *et al.*[104] employed ML and bioinformatics techniques to identify genes related to ferroptosis in PD by analyzing DEGs. A total of 109 PD-related ferroptosis DEGs were identified after combining three cohorts (GSE7621, GSE202665, GSE20146) from the National Center for Biotechnology Information (NCBI) GEO and FerrDb V2 databases. The researchers also identified natural products with anti-PD effects that could be used for treatment. ML algorithms revealed six hub genes (*IL6, ATG7, TLR4, ADIPOQ, FADS2,* and *PTGS2*) and

29 overlapping genes. In addition, the study screened 263 natural product components and constructed an "Overlapping Genes-Ingredients" network.

Xin *et al.*[105] identified important immune-related hub genes in PD using ML and developed a diagnostic model based on the GEO (GSE8397) database, which includes gene expression data from 15 healthy and 24 PD subjects' substantia nigra (SN) samples. DEGs related to PD were identified using WGCNA and DEA. LASSO and multiple SVM-RFE ML algorithms were used to identify hub genes (*TTD19, DLD, DLK1*, and *IARS*). LR was then employed to develop a PD classification model, and its accuracy was tested in three unrelated cohorts: GSE20292 (18 healthy SN samples and 11 PD SN samples), GSE7621 (nine healthy SN samples and 16 PD SN samples), and GES49036 (eight healthy SN samples and 15 PD SN samples). The AUC scores for *DLK1*, *DLD*, and *TTC19* exceeded 70% in GSE8397 and all three external validation datasets, indicating strong accuracy. In GSE8397 and one external validation cohort, *IARS* showed an AUC greater than 70%, with values ranging from 50% to 70% in the other two datasets, suggesting its research value. The joint diagnostic model, developed with the four immune-related PD hub genes, demonstrated an AUC greater than 90% in GSE8397 and all three external validation datasets.

Zhang *et al.*[106] employed interpretable DL approaches to identify important genes and biomarkers related to PD using gene expression data from a GEO dataset. Their approach yielded promising results, achieving an AUC of 73% and an F1-score of 71%, effectively distinguishing PD subjects and providing valuable insights into relevant biological pathways. Using interpretable DL models, the authors identified important biomarkers (*XK, TUBA4B, TP53,* and *PDK1*) and their associated biological pathways linked to PD. Notably, the *XK* gene showed a strong correlation with PD.

Ameli *et al.*[107] proposed that the integration of Singular Vector Feature Selection and the RF algorithm can be effectively utilized to analyze single-nucleotide polymorphism (SNP) data and identify PD biomarkers. To assess the reproducibility of these biomarkers, they gathered five SNP datasets from the Database of Genotypes and Phenotypes, including dataset IDs phs000394, phs000126, phs000089, phs000089, and phs000048, with sample sizes of 1001, 2082, 1741, 526, and 886, respectively. Their analysis revealed that, on average, 93% of the SNPs identified in one dataset were not repeated in the others. However, when multiple datasets were integrated, the replication gap dropped to 62%. Furthermore, these researchers identified four SNPs directly linked to PD and 50 SNPs indirectly linked to PD in the literature.

Banou *et al.*[108] applied ML algorithms to analyze single-cell RNA-sequencing data related to PD and to explore their association with hyperbaric oxygen therapy (HBOT). The dataset included 4495 cells (2518 from control and 1977 from PD groups), with expression profiles across 18,098 genes. FSS was performed using the XGB. The authors employed 15 ML algorithms, including LR, KNN, NB, DT, RF, gradient boosting machines, SVM, quadratic discriminant analysis, ridge classifier, LDA, extreme gradient boosting machine (LightGBM), CatBoost, AdaBoost, ETs, stochastic gradient descent, and a dummy classifier, to classify cells from PD-affected subjects versus healthy subjects. Using the top 100 genes, LR outperformed the other ML algorithms in terms of accuracy, precision, F1-score, MCC, and Kappa, achieving 99.59%, 99.43%, 99.53%, 99.17%, and 99.16%, respectively. The highest AUC (100%) and recall (100%) were achieved by CatBoost and NB classifiers, respectively. Genes, such as *MAP2*, *WSB1*, and *CAP2*, among others, were found to be highly related to PD and demonstrated notable correlation with HBOT.

Kumar *et al.*[109] employed data-mining techniques to identify novel microRNA (miRNA) biomarkers and subsequently developed an ML model for PD diagnosis based on the identified biomarkers. The training dataset comprised 112 miRNAs (56 PD and 56 non-PD). After filtering, the number of features was reduced from 16,299 to 61. Ten-fold cross-validation tests yielded the following accuracies: 87.50% for RF, 91.07% for the Hoeffding Tree, 91.96% for NB, 90.18% for MLP, and 95.65% for the Sequential Model. As the Sequential Model outperformed the others, its performance was validated using an independent dataset, achieving 93.3% accuracy.

By analyzing transcriptome data of 117 subjects (56 PD and 61 healthy) from the GEO database and validating the findings through reverse transcription-quantitative polymerase chain reaction (RT-qPCR), Peng *et al.*[110] discerned *EAF2* as a significant gene in PD, consistently showing downregulation in PD subjects compared to healthy subjects. DEA, WGCNA, and three ML algorithms (RF, LASSO, and SVM-RFE) were applied to identify critical genes related to PD. The diagnostic performance of *EAF2* showed an AUC of 74.5% in the training dataset, 75.2% in the validation dataset, and 84.2% in blood samples, indicating its association with PD pathology.

Teng *et al.*[111] explored and evaluated critical genetic biomarkers for PD diagnosis. DEA was conducted on the PD datasets obtained from GEO database (GSE20141 – 18 tissue samples, GSE18838 – 28 blood samples, GSE20295 – 93 tissue samples, and GSE6613 – 102 blood samples) consists of both PD and control tissue samples. Using two

ML methods, LASSO and SVM, the study identified *GPX2*, *ZNF556*, and *CR1* as genes crucial to PD pathogenesis, suggesting these may serve as potential diagnostic biomarkers. In the validated blood sample dataset, the combined assessment of these three genes outperformed individual gene assessments, achieving an AUC of 70.1%. Samples from peripheral blood mononuclear cells exhibited consistent diagnostic value for each gene, with the combination yielding improved performance with an AUC of 80.1%.

Yan *et al.*[112] performed DEA of the GSE8397 dataset (18 control and 29 PD) from the GEO database and selected 11 key N6-methyladenosine (m6A)-related genes to develop two ML models using SVM and RF algorithms. The RF model achieved an AUC value of 100%, outperforming the SVM model, which achieved an AUC value of 98.3%. In the final stage, the RF model was visualized, and four m6A-related genes (*YTHDC2*, *LRPPRC*, *HNRNPC*, and *IGFBP3*) were identified as major candidates for the "nomogram model," leading to accurate recognition of PD. They also identified two distinct m6A clusters in PD, each characterized by contrasting immune features, by analyzing the information from the 11 m6A-related genes.

Yang *et al.*[113] identified four genes related to aging by training an ML model using whole-blood RNA-sequencing data from 24 subjects (13 healthy and 11 PD). By employing ML algorithms, such as LASSO, SVM, RF, and Ridge regression, along with LASSO regression and Venn diagrams, they identified four genes as significant PD biomarkers. These genes were further assessed using three additional datasets from GEO and RT-qPCR in peripheral blood mononuclear cells from 10 PD and 10 healthy subjects. ROC curve analysis demonstrated that aging-related DEGs could effectively distinguish PD from healthy subjects, with an AUC score exceeding 70%, indicating their potential as PD diagnostic biomarkers.

Yu *et al.*[114] aimed to identify the most relevant gene in each PD locus and uncover novel mechanisms implicated in PD. An XGB ML model was trained using 212 genes (seven well-known genes labeled as positive and 205 genes not associated with PD labeled as negative) from Genome-Wide Association Study loci, utilizing transcriptomic, genomic, and epigenomic data from mDANs and brain tissues. Sixty-three percent of genes were assigned a probability score greater than 75% and were therefore considered related to PD.

Genetic research has revolutionized the understanding of PD, shifting the focus from clinical symptoms to molecular mechanisms. The identification and application of genetic biomarkers hold great promise for early diagnosis, risk prediction, and targeted treatment. Future advancements in genetic screening, personalized medicine, and gene therapy could significantly improve outcomes for individuals living with PD. However, much work remains in translating genetic findings into tangible clinical applications.

3.2.5. Gut biomarkers and AI methods

Gut biomarkers for PD are mainly classified under both biochemical and genetic markers, as well as areas, such as microbiome and metabolomic profiling. While not a completely separate category, gut-related biomarkers can also be studied through neuroimaging and clinical observations. Here, we explore research conducted so far that utilizes gut biomarkers in conjunction with AI methods for PD detection, monitoring, and classification of PD subjects from healthy subjects.

Pietrucci *et al.*[115] investigated the role of GM in PD and identified common microbial alterations that could potentially predict PD. The authors applied three ML algorithms—RF, neural network, and SVM—to analyze 846 metagenomic samples (472 PD and 374 healthy). The RF algorithm outperformed the others, achieving an AUC score of 80% ± 1% and 71% accuracy, as compared to AUC score 67% ± 3% for the neural network and 54% ± 8% for the SVM. RF also identified a subset of 22 microbial families capable of distinguishing PD and healthy subjects.

Qian *et al.*[116] created the first GM gene catalog related to PD based on metagenomic sequencing. They collected GM genes from the feces of 40 Chinese PD subjects and their healthy counterparts using shotgun metagenomic sequencing (SMG). By applying the mRMR technique, 25 gene markers were selected from 51,816 genes as potential PD biomarkers. When these 25 biomarkers were used in an SVM classifier, the model achieved: 89.6% AUC, 90% sensitivity, and 75% specificity. The identified genes were further validated using real-time PCR in a separate dataset of 78 PD and 75 healthy subjects, achieving an AUC of 90.5%, 86% sensitivity, and 77% specificity. An AUC of 83.1%, sensitivity of 85%, and specificity of 78% were observed when differentiating 78 PD and 40 multiple system atrophy subjects. Furthermore, 90.1% AUC, 90% sensitivity, and 88% specificity were achieved in differentiating 78 PD from 25 AD subjects.

Lubomski *et al.*[117] developed a PD prediction model to assess GM compositional changes in combination with macronutrient consumption. They conducted a cross-sectional evaluation involving 184 subjects (103 PD and 81 household controls). RF- and SVM-based models were developed to aid in identifying PD. The RF model, which incorporated taxonomic data at the genus level and the contribution of carbohydrates to total energy intake,

exhibited the highest predictive performance, with an AUC score of 74%.

Nie *et al.*[118] investigated the relationship between PD and GM, and developed a PD predictive model by analyzing 2269 16S ribosomal RNA (16S rRNA) specimens (896 healthy and 1373 PD) and 236 SMG specimens (114 healthy and 122 PD). Both 16S rRNA and SMG analyses identified five genera (*Bifidobacterium, Akkermansia, Streptococcus, Desulfovibrio,* and *Lactobacillus*) with increased abundance, and five genera (*Lachnospira, Faecalibacterium, Roseburia, Blautia,* and *Prevotella*) with decreased abundance in PD patients. Moreover, RF models based on 11 genera achieved classification accuracy exceeding 80% in distinguishing PD from healthy subjects. A separate RF model based on six inflammation-related genes outperformed the former, with accuracy >90%. These outcomes highlight the role of inflammation in PD prediction and treatment.

To examine the role of gut dysbiosis in PD progression, Nishiwaki *et al.*[119] developed RF models to predict 2-year PD progression based on GM from 165 PD subjects. The AUC-ROC scores of the GM-based models for H&Y stages 1 and 2 were 79.9% and 70.5%, respectively. In addition, the GM profile predicted the progression of MDS-UPDRS III scores in early-stage PD with an AUC-ROC of 72.8%. An increase in mucin-degrading genus Akkermansia and a decrease in short-chain fatty acid-producing genera, *Blautia, Faecalibacterium,* and *Fusicatenibacter,* were associated with faster PD progression.

The objective of the study conducted by Sánchez[120] was to discover potential biomarkers by comparing the GMs of 20 control and 20 PD subjects, identifying candidate taxa, gene families, and pathways that could offer insights into variables important for early PD detection. This was achieved using various metagenomics programs alongside five ML algorithms (DT, RF, NB, SVM, and KNN). The study identified key features, including an overexpression of Myo-chiro and scyllo-inositol degradation pathways and a higher abundance of Lactococcus phage in PD patients.

Boodaghidizaji *et al.*[121] used ML algorithms to analyze the patterns of stool microbiota as well as their response to fiber as a diagnostic tool for lifelong inflammatory diseases. They applied ML algorithms to differentiate between PD, ulcerative colitis, Crohn's disease, HIV, and healthy subjects, with and without fiber treatment, achieving classification accuracy of up to 95%. In addition, ML algorithms achieved accuracy up to 90% when microbiome data were used to predict ulcerative colitis and Crohn's disease.

Dhatrak[122] explored the application of ML predictive technologies to analyze the compositions of GMs and their alterations in PD subjects. The study utilized a dataset of 17 randomly selected fecal samples (nine PD and eight healthy) obtained from the European Nucleotide Archive database under the project PRJEB27564. The performance of two ML algorithms, RF and linear support vector classifier (LSVC), was evaluated using the QIIME 2 classifier and various performance metrics. With RF, the following results were achieved: accuracy = 66%, recall = 66%, precision = 66%, F1-score = 88%, and specificity = 66%. For LSVC, the results were: accuracy = 66%, recall = 100%, precision = 66%, F1-score = 82%, and specificity = 33%.

Li *et al.*[123] thoroughly assessed the performance of GM-based ML classification algorithms across 20 diseases, using 83 case-control cohorts (9708 samples in total) across five main disease groups. Each disease was represented by at least two cohorts. In single-cohort classifiers, high predictive accuracies (~77% AUC) were achieved in within-cohort validation, but lower accuracies were observed in cross-cohort validation, excluding intestinal diseases, where AUC was around 73%. To improve validation scores for non-intestinal diseases, samples from multiple cohorts were used to train combined-cohort classifiers. The study also predicted the sample size needed to reach more than 70% validation accuracies. Additionally, for intestinal diseases, higher validation performance was achieved by classifiers using metagenomic data than 16S amplicon data.

Romano *et al.*[124] conducted a meta-analysis of PD GM studies with 4489 samples from 11 countries across four continents, reporting on the fecal microbiomes of PD subjects and controls using both 16S amplicon sequencing (3165 samples) and SMG (1324 samples). They trained the ML models on various datasets and concluded that GM is associated with both PD diagnosis and its treatment.

Zhang *et al.*[125] proposed an interpretable and accurate neural network approach for PD prediction and biomarker discovery using whole metabolomics datasets without initial FSS. Samples were collected from two cross-sectional studies: the EPIC study (GC-MS: 36 PD and 39 control; capillary electrophoresis-mass spectrometry: 39 PD and 39 control; LC-MS[+]: 39 PD and 39 control; LC-MS[−]: 36 PD and 37 control; composite: 35 PD and 37 control) and the National Health Service study (LC-MS[+]: 80 PD and 56 control; LC-MS[+]: 138 PD and 56 control). The neural network approach demonstrated significantly superior performance in predicting PD from blood plasma metabolomics data, achieving a mean AUC exceeding 99.5%, outperforming five other ML methods. XGB and LR showed similar performance with AUC-ROC scores of 97.0% ± 2.8% and 96.8% ± 3.7%, and AUC-precision-recall scores of 96.8% ± 3.1% and 96.9% ± 3.7%, respectively. In contrast, RF, LDA, and SVM classifiers showed relatively

lower performance, with AUC-ROC and AUC-precision-recall values of 82.9% ± 9.9% and 83.6% ± 9.9% for RF, 64.7% ± 9.3% and 66.1% ± 11.1% for SVM, and 68.1% ± 9.1% and 63.4% ± 11.9% for LDA. Based on the MCC score, the neural network approach outperformed the other classifiers, with a score of 91.8% ± 8.6%, compared to 81.5% ± 13.2% for LR, 78.7% ± 11.9% for XGB, 43.3% ± 19.2% for RF, 27.2% ± 15.2% for LDA, and 21.3% ± 15.5% for SVM.

Li *et al.*[126] developed an AI-guided, gut micro-environment-triggered imaging sensor to accurately and non-invasively identify the PD stages by monitoring α-syn using a DL algorithm. In mouse experiments, PD stages were classified as 0 (early), 1 (middle), and 2 (advanced). Initially, the dataset included samples from 10 normal, nine midterm PD, and 16 advanced PD mice; however, after data augmentation, the dataset expanded to 40 normal, 40 midterm PD, and 60 advanced PD mouse samples. The proposed CNN model, based on AlexNet, outperformed five benchmark ML algorithms (DT, SVM, KNN, LDA, and NB), achieving over 98% testing accuracy.

Zhao *et al.*[127] performed a meta-analysis to examine the role of GM in PD and its diagnostic potential. They integrated six *16S rRNA* gene datasets from five different studies, comprising 456 healthy and 550 PD samples. The analysis identified reduced levels of butyrate-producing taxa (*Faecalibacterium*, *Roseburia*, *Coprococcus_2*) and increased levels of *Akkermansia* and *Bilophila* in PD. Using a network-based approach, the study identified microbial biomarkers for PD and developed a classification model based on RF using 11 key genera, demonstrating strong diagnostic potential. The optimized PD classification model achieved 100% accuracy and 100% AUC on the training dataset, and 80.2% accuracy and 86.4% AUC on the test dataset.

Rojas-Velazquez *et al.*[128] utilized four PD-related datasets from the NCBI, focusing on stool samples, and identified a microbiome signature for diagnosing PD using ML. By employing the Recursive Ensemble Feature Selection algorithm, 84 features were identified from the discovery dataset (PRJEB14674–345 samples: 134 healthy and 211 PD), achieving an accuracy exceeding 80%. The ET classifier demonstrated a diagnostic accuracy with an AUC-ROC of 74% in validating the discovery dataset. During testing, AUC-ROC scores of 64% for PRJEB14674 (345 samples: 134 healthy and 211 PD), 71% for PRJEB27564 (266 samples: 130 healthy and 136 PD), and 62% for PRJNA594156 (300 samples: 103 healthy and 197 PD) were achieved.

Yu *et al.*[129] developed an efficient DL-based prediction method for accurately diagnosing PD by analyzing GM data. The study utilized data from 39 PD subjects and their respective 39 healthy spouses. For FSS, a pre-processing technique called combined ranking using RF scores and PCA contributions was applied, followed by the LSIM (LSTM-penultimate to SVM Input Method) for classifying PD subjects. A soft voting mechanism was then used for final PD prediction. The Parkinson Gut Prediction method demonstrated an AUC of 92%, a mean accuracy of 85%, and an ROC of 92%.

These studies indicate that by leveraging gut biomarkers and AI methods, there is significant potential for improving the detection, monitoring, and management of PD. As research progresses, AI-powered approaches are set to become key tools in clinical practice, thereby enhancing patient care and outcomes in PD.

4. Discussion

This section discusses some important parameters used to evaluate the studies related to PD. The aim of this analysis is to explore how these parameters impact various aspects of PD diagnosis and treatment. The parameters under consideration include research objectives, the strengths and weaknesses of AI methods, existing innovations, and their practical applications in the medical field.

4.1. Challenges in selecting suitable biomarkers

While assessing different types of biomarkers and AI methods for PD detection, we observed several challenges due to the complex and multifactorial nature of PD. Both biomarkers and AI methods offer distinctive advantages but also have limitations. Some key challenges associated with using different types of biomarkers and AI methods in PD detection include:

(i) Variability and heterogeneity of PD: PD manifests differently across individuals, with varying symptoms, disease progression rates, and responses to treatment. Therefore, no single biomarker can comprehensively represent PD or its progression. As a result, it is challenging to identify reliable and consistent biomarkers that perform well for all affected PD subjects.

(ii) Lack of early detection biomarkers: many existing biomarkers tend to detect PD at later stages of the disease, after significant neuronal damage has already occurred. Early-stage biomarkers are still under investigation but have not yet been clinically established. Biochemical biomarkers, such as CSF hold potential for early detection but require further validation to ensure reliability and specificity for PD. In addition, biomarkers often suffer from poor specificity, meaning they may not distinguish PD from other NDs like AD. Similarly, some biomarkers may

lack the necessary sensitivity to detect PD in its early stages or in individuals with atypical presentations. Certain fluid-based biomarkers, such as those found in CSF, require invasive procedures, such as lumbar punctures, which can be uncomfortable for patients and limit their practical use in routine screening for PD. On the other hand, neuroimaging biomarkers are non-invasive but can be costly, time-consuming, and require specialized equipment and expertise.

(iii) Standardization of PD biomarkers: standardization of many PD biomarkers is still an issue. The features extracted from imaging can vary depending on the type of machine, the scanning method, and how the results are interpreted. Moreover, many biomarkers still lack robust clinical validation in large, diverse cohorts, which is necessary to establish their clinical utility and reliability for PD diagnosis and prognosis. Standardization is important to ensure that the findings from these techniques can be widely applied and trusted across various research and clinical environments.

4.2. Challenges in applying AI methodologies

The performance of AI algorithms for PD detection is influenced by several factors, including the quality of the data, the choice of model, hyperparameter settings, and data pre-processing. Below are the key factors that significantly affect how well AI models perform in PD detection:

(i) Data quality: accurate and comprehensive labels are critical in supervised learning for training and evaluating AI models. Inaccurate or missing labels can lead to poor model performance. Medical data, particularly from clinical assessments or imaging, may contain noise or outliers that also affect AI algorithm performance and, consequently, the model's ability to generalize. Imbalanced datasets, often suffering from class imbalances, can bias predictions toward the majority class, causing poor detection of PD cases. The presence of missing values in the dataset can also reduce model performance.

(ii) Feature selection: selecting relevant features is important. Irrelevant or redundant features can reduce the model's ability to generalize and increase computational costs. However, high-dimensional datasets can also lead to overfitting.

(iii) Model selection: different AI algorithms are suitable for different data types. For example, SVM performs well with high-dimensional datasets, such as genetic data or neuroimaging features. RF is robust to noise and effective with diverse data types, such as clinical, biomarker, or demographic data. CNNs are well-suited for imaging data due to their ability to learn spatial hierarchies of features. RNNs or LSTM networks are better for time-series data,[130] such as motor symptom progression over time. More complex models may achieve better results but are more prone to overfitting when training data is limited. Simpler models, for example, SVM or RF, may generalize better on smaller or less noisy datasets.

(iv) Hyperparameter tuning: most AI algorithms have hyperparameters (e.g., kernel type in SVM, number of trees, rate of learning, maximum depth) that must be optimized for good performance. Improper tuning can lead to poor model performance, overfitting, or underfitting.

(v) Training data size: AI models, especially DL algorithms, require large datasets to achieve high performance. With small datasets, models tend to memorize training data and fail to generalize to external testing data.

(vi) Cross-validation and testing: cross-validation helps ensure the model generalizes well to unseen external testing data and reduces the likelihood of overfitting to a specific training set. It is also important to evaluate AI models on data representative of real-world conditions.

(vii) Temporal changes and disease progression: models incorporating time-series data or temporal information (e.g., gait, motor fluctuations) often require specialized algorithms, such as RNNs, LSTMs, or reinforcement learning. PD models using longitudinal data need to account for variability over time.

(viii) Bias and fairness: AI model capabilities are limited by the quality of the training data. If training datasets for PD detection lack diversity (in age, ethnicity, gender, comorbidities), AI systems may perform poorly for underrepresented groups, leading to biased diagnoses, healthcare access, and health disparities.[130] Efforts are needed to ensure AI systems are fair and unbiased, treating all patients equitably. This includes developing diverse, representative datasets and actively testing AI models to assess their performance across different demographic groups.

4.3. Ethical and clinical implications

Ienca and Ignatiadis[131] emphasized that while AI holds significant promise for advancing brain research by optimizing and developing effective neurotechnology frameworks, it also raises important ethical and clinical concerns. The impact of AI on scientific validity and neuroethics remains uncertain.

In PD detection, AI systems require access to sensitive data, such as medical histories, neuroimaging scans, and

genetic information. Ensuring secure data storage and protecting patient privacy are crucial, with AI systems needing to comply with regulations, such as the Health Insurance Portability and Accountability Act and the General Data Protection Regulation. Patients must provide informed consent for the use of their data, and transparency about how their data is handled is essential.[130] Given that AI models are trained using patient data, it is vital that patients fully understand how their data will be utilized. Clear, accessible information should be provided, and patients should be encouraged to ask questions before consenting to participate in AI-based studies or diagnostic tools.

4.4. Future directions

While AI has made considerable advances in PD research, future efforts are crucial to overcome existing challenges and fully harness AI's potential in patient care. Key research areas include:

(i) Integration of multimodal data: PD is a multifactorial disease, and a single modality may not provide a comprehensive understanding of its progression. Integrating data from different biomarker modalities, such as neuroimaging, clinical, biochemical, and genetic could facilitate early diagnosis and improve predictions of disease progression.

(ii) Real-time monitoring and predictive analytics: traditional PD monitoring largely depends on clinical visits. AI, in combination with wearable devices (e.g., smartwatches), can track real-time data, such as motor fluctuations and sleep patterns to predict disease progression and support personalized treatment adjustments.

(iii) XAI for clinical decision support: developing XAI models can help clinicians interpret AI predictions, improve trust, and support more informed decision-making. For instance, algorithms that highlight key features, such as a combination of motor symptoms, voice analysis, or affected brain regions can assist clinicians in interpreting results and guiding treatment plans.

(iv) AI in personalized treatment planning: PD affects individuals differently, and treatment responses can vary significantly. AI can analyze patient-specific data (e.g., genetics, lifestyle, disease severity) to recommend customized therapies, potentially improving treatment efficacy and minimizing side effects.

(v) AI in early detection through biomarker discovery: detecting PD in its early stages is challenging, as symptoms often appear after substantial neuronal damage. AI can facilitate the discovery of early biomarkers by analyzing large datasets across various modalities to identify molecular markers that precede clinical symptoms.

(vi) Improved AI for non-motor symptom monitoring: both motor and non-motor symptoms are significantly associated with disease progression. AI tools capable of monitoring non-motor symptoms, such as cognitive changes or depression, through smart home devices or wearable sensors could provide deeper insights into patient status.

(vii) Collaboration between AI experts, clinicians, and patients: a gap often exists between AI model development and its practical application in clinical settings. Without collaboration among AI researchers, clinicians, and patients, models may lack clinical relevance or overlook patient-centered concerns. Close interdisciplinary collaboration is essential to ensure AI models are clinically useful, patient-centric, and applicable in real-world settings.[130]

4.5. Limitations of the study

Despite providing a detailed synthesis of the most relevant information on AI methods for PD diagnosis, this review has certain limitations. Although we aimed to address most of the research questions outlined in Section 3.1, some information could not be included due to its absence in the existing literature.

(i) In several studies, the number of subjects affected and unaffected by PD was not clearly stated. This missing information creates uncertainty for other researchers regarding the actual number of individuals affected by PD worldwide

(ii) We found that the sizes of the training and testing datasets were often not reported, making it difficult for other researchers to replicate the developed models for PD progression

(iii) Details of performance metrics were also missing in several studies, hindering the ability to evaluate which AI algorithms perform best for PD detection. Consequently, despite some studies reporting impressive classification results, they were excluded from this review due to the lack of necessary performance details

(iv) In a few studies, inconsistencies were observed between the abstract and results sections, with different values reported for performance metrics. This inconsistency adds to the confusion among researchers

(v) During our review of the literature, we also noted a lack of collaboration between clinicians and AI researchers, which may limit the clinical relevance and practical application of the proposed AI models.

5. Conclusion

The intricate nature of PD arises from complex interactions between environmental and genetic factors,

making it difficult to accurately identify its underlying mechanisms.

Recent advancements in AI have positioned these technologies as powerful tools for analyzing and interpreting medical data. By integrating various types of biomarkers with AI techniques, early diagnosis and enhanced treatment strategies for PD can be facilitated. However, the implementation of these methodologies presents several challenges, including issues related to data quality and diversity, model interpretability, and the need for interdisciplinary collaboration among healthcare professionals and researchers.

Findings from this review indicate that AI can achieve diagnostic accuracies exceeding 90% for PD, while also reducing the time required for diagnosis. Moreover, AI approaches have demonstrated superior prognostic capabilities compared to traditional diagnostic methods. Ultimately, this review provides valuable insights for both medical professionals and researchers into the potential and challenges of leveraging AI techniques to enhance the diagnosis and management of PD.

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Conflict of interest

The authors declare that they have no competing interests.

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Further disclosure

The authors declare that no AI and AI-assisted technologies were used in conducting key aspects of the research, such as generating scientific insights, analyzing or interpreting data, or drawing scientific conclusions.

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