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Review Article

Artificial intelligence and multiomics integration for Parkinson's disease drug development

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ABSTRACT

Recent advances underscore the potential of integrating multiomics, such as genomics, transcriptomics, proteomics, and metabolomics, and artificial intelligence to overcome limitations regarding early diagnosis and treatment of Parkinson's disease. Developing a comprehensive view of the complex molecular landscape of Parkinson's disease through artificial intelligence algorithms would enable the processing of extensive multiomics datasets. Applying these integrative technologies to Parkinson's disease research would improve early diagnosis, support personalized therapeutic strategies, and drug discovery. This review explores the transformative potential of integrating multiomics and artificial intelligence in Parkinson's disease, outlining a framework to advance diagnosis, treatment, and drug development in neurodegenerative diseases.

Keywords: Artificial intelligence, Drug discovery, Multiomics, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor symptoms, such as bradykinesia, rigidity, and tremor, as well as nonmotor symptoms, including cognitive decline and mood disturbances (Obeso et al., 2017). PD neuropathology is characterized by the degeneration of dopaminergic neurons in the substantia nigra, leading to dopamine deficiency in the striatum (Obeso et al., 2017). PD is the second-most prevalent neurodegenerative disease globally, with an increasing incidence in the aging population (de Lau and Breteler, 2006; Willis et al., 2022). The etiology of PD is multifaceted, encompassing genetic, environmental, and lifestyle factors, yet its underlying pathophysiology remains incompletely defined (Ascherio and Schwarzschild, 2016). Current treatments for PD, including levodopa and dopamine agonists, are based on symptom management to alleviate motor symptoms; however, these treatments fail to modify disease progression and halt neurodegeneration. Furthermore, prolonged use often leads to complications like dyskinesias and motor fluctuations (Schapira et al., 2009). Traditional drug development approaches to PD are beset with obstacles, such as high clinical trial failure rates and a lack of reliable biomarkers for early diagnosis and monitoring, highlighting the need for innovative therapeutic approaches (Jankovic, 2005). Integrating multiomics methodologies, such as genomics, transcriptomics, proteomics, and metabolomics, with artificial intelligence (AI), offers a promising avenue to address these limitations. Multiomics approaches facilitate comprehensive biological profiling across molecular levels, yielding insights into complex pathophysiological mechanisms that single-omics methods cannot adequately capture (Hasin et al., 2017). The use of AI-driven analyses for clinical outcomes, particularly through machine learning (ML) and deep learning (DL), can efficiently process large-scale datasets to facilitate pattern recognition and predictive modeling. This integrative paradigm has enabled advancements in oncology research, improving patient stratification, biomarker discovery, and drug target identification (Bhinder et al., 2021).

The application of AI and multiomics has successfully led to the identification of early biomarkers and potential therapeutic targets in Alzheimer's disease (AD), providing insights into the

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disease mechanism (De Jager et al., 2018). Extending these integrative methodologies to PD research could unlock a realm of possibilities, such as discovering novel molecular pathways implicated in PD through multiomics data, identifying new biomarkers, and predicting disease progression by AI-driven analysis to enable early and accurate diagnoses (Zhang, 2022). Moreover, AI-facilitated drug discovery platforms can expedite the identification of viable drug targets, accelerating the development of disease-modifying therapies. By stratifying patients according to molecular profiles, researchers can create therapeutic strategies tailored to specific disease mechanisms, thus improving clinical outcomes and minimizing treatment side effects (Doherty et al., 2023). Consequently, this review comprehensively examines these methodologies and underscores the transformative potential of AI and multiomics in enhancing PD diagnosis, treatment, and patient care.

PARKINSON'S DISEASE

Overview of PD

PD was first described by James Parkinson in 1817 (Parkinson, 2002). It is characterized by motor symptoms including resting tremor, bradykinesia, and postural instability, which primarily arise from dopaminergic neuronal loss in the substantia nigra and subsequent dopamine depletion in the striatum (Dauer and Przedborski, 2003; Kouli et al., 2018). Beyond motor deficits, PD leads to nonmotor symptoms like cognitive decline, mood disorders, and autonomic dysfunction (Chaudhuri et al., 2006). The pathogenesis of PD is multifactorial, involving intricate interactions between genetic susceptibility and environmental factors. Mutations in genes such as *SNCA*, *LRRK2*, and *PRKN* have been linked to PD development in familial and sporadic cases (Klein and Westenberger, 2012). Although the exact causes of PD remain unclear, mitochondrial dysfunction, oxidative stress, and environmental toxins are key contributors (Ascherio and Schwarzschild, 2016; Rocha et al., 2018).

The global prevalence of PD ranges from 300 to 1,400 per 100,000 individuals, and varies by region (Ou et al., 2021; Pringsheim et al., 2014). PD incidence markedly increases with age, primarily affecting those over 60 years, although early-onset PD (< 50 years old) has been documented and linked to genetic mutations (Willis et al., 2022). The burden of PD is expected to rise significantly due to global aging, straining health care systems. From 6.2 million people living with PD in 2015, the global patient population is projected to rise dramatically, reaching 12.9 to 14.2 million by 2040, highlighting the need for improved diagnostics, treatments, and preventive strategies (Dorsey and Bloem, 2018).

Traditionally, PD is diagnosed according to clinical motor symptoms—including bradykinesia, rigidity, and tremor—as based on the UK Parkinson's Disease Society Brain Bank criteria (Clarke et al., 2016). However, these criteria have notable limitations, especially in the early disease stages when motor symptoms are mild or absent (Tolosa et al., 2021). Consequently, PD is often diagnosed after major neurodegeneration has occurred, restricting treatment effectiveness (Adler and Beach, 2016). Recent advances in neuroimaging have enhanced diagnostic accuracy, notably through dopamine transporter imaging using single-photon emission computed tomography or positron emission tomography (Porter et al., 2020). These techniques enable visualization of striatal dopaminergic deficits and can aid diagnosis when symptoms are unclear (Brooks, 2010). Additionally, studies have explored the application of magnetic resonance imaging (MRI) and transcranial sonography as noninvasive modalities to detect structural brain changes associated with PD (Saeed et al., 2017). The identification of reliable PD biomarkers has become a major global research priority, with ongoing studies examining biological fluids, such as cerebrospinal fluid (CSF), blood, and saliva. Biomarker proteins such as alpha-synuclein (α-syn), DJ-1, and neurofilament light chain have been investigated for early diagnosis and disease monitoring (Kang et al., 2013; Mollenhauer et al., 2019). Nevertheless, no single biomarker has yet to be validated for routine use, highlighting the need for further research.

History and development of PD

The treatment for PD has evolved over the past century, with diverse therapies addressing its complex symptoms. From early efforts with anticholinergic medications to contemporary dopamine-replacement therapies and advanced surgical interventions, the evolution of PD treatment reflects an enhanced understanding of its underlying pathophysiology and an ongoing pursuit of more effective and safer therapeutic options.

Levodopa

Levodopa remains the cornerstone of PD treatment and is widely recognized as the most effective medication for managing motor symptoms. Introduced in the 1960s, it revolutionized treatment by directly addressing the underlying dopaminergic deficit in the brain, significantly improving patients' quality of life by reducing motor symptoms (Brooks, 2008; Katzenschlager and Lees, 2002). Typically, levodopa is administered in combination with peripheral decarboxylase inhibitors, such as carbidopa or benserazide, this combination markedly enhances levodopa's therapeutic efficacy (Rinne and MÖlsÄ, 1979). However, chronic therapy can result in motor fluctuations (on-off phenomena) and dyskinesias, prompting the ongoing development of alternative treatments and adjunctive therapies (Nutt et al., 1984).

Dopamine Agonists

Dopamine agonists were introduced to reduce the long-term complications from levodopa therapy by directly stimulating dopamine receptors, mimicking dopamine's effects (Parkes et al., 1976). Bromocriptine was the first dopamine agonist introduced for PD treatment in the 1970s, followed by agents such as pramipexole, ropinirole, and rotigotine with improved safety profiles (Bonuccelli et al., 2009). They are effective as monotherapy in early PD, and as adjunct therapy with levodopa in advanced disease stages, particularly beneficial for managing motor fluctuations and reducing dyskinesia (Holloway et al., 2004). Nevertheless, dopamine agonists have distinct adverse side effects, including impulse control disorders (eg, gambling, hypersexuality), daytime somnolence, and hallucinations, that potentially restrict their clinical utility, especially in older patients (Weintraub et al., 2010).

Monoamine Oxidase-B Inhibitors

Monoamine oxidase-B (MAO-B) inhibitors function by inhibiting dopamine degradation in the brain, thereby extending its availability and improving motor symptoms (Riederer and Laux, 2011). Selegiline was the first MAO-B inhibitor approved for PD treatment in the 1980s, followed by rasagiline (Olanow et al., 2009). MAO-B inhibitors are commonly used in early PD as monotherapy or adjunctively with levodopa in advanced stages to enhance efficacy and mitigate motor fluctuations (ParkinsonStudyGroup, 1989). Their mild side effects make them suitable for elderly patients, but the efficacy of monotherapy with these drugs is generally lower than that of levodopa or dopamine agonists (Chahine and Stern, 2011).

Catechol-O-Methyltransferase Inhibitors

Catechol-O-methyltransferase inhibitors, including entacapone and tolcapone, enhance levodopa efficacy by inhibiting its peripheral metabolism (Brooks and Sagar, 2003). Introduced in the 1990s, they boost brain levodopa, extending its effect and reducing motor fluctuations (Kaakkola, 2000). Entacapone is frequently used in triple therapy with levodopa/carbidopa and has become a standard treatment strategy for managing motor complications in advanced PD (Brooks, 2008). While tolcapone usage is restricted due to hepatotoxicity concerns, entacapone has a more favorable safety profile (Borges, 2003). Despite these advantages, catechol-O-methyltransferase inhibitors lack effectiveness as monotherapy and are exclusively utilized in combination with levodopa to optimize therapeutic outcomes (Nyholm et al., 2003).

Deep Brain Stimulation

Deep brain stimulation (DBS) is a prominent surgical intervention for advanced PD who do not respond well to medication, gaining recognition since the 1990s (Bronstein et al., 2011). DBS involves implanting electrodes in brain regions, such as the subthalamic nucleus, to stimulate neural activity via a pulse generator (Okun, 2012). Clinical trials have consistently demonstrated that DBS significantly alleviates motor symptoms, reduces medication requirements, and enhances the quality of life for patients with advanced PD (Weaver et al., 2009). Nonetheless, DBS carries inherent risks, like infection, hemorrhage, and cognitive issues, requiring careful patient selection and monitoring (Kenney et al., 2007). Overall, DBS constitutes a substantial advancement in PD treatment, offering meaningful therapeutic options to individuals who have exhausted pharmacological approaches (Volkmann et al., 2009).

Immunotherapy for PD: Lessons From Research Related to AD

Recent approvals of antiamyloid antibodies for AD, such as aducanumab and lecanemab, indicate that biologics can succeed when trials are anchored by biomarker-defined patient selection and measurable target engagement, which also enables more systematic monitoring and mitigation of safety risks (Budd Haeberlein et al., 2022; Miles and Masters, 2025). These findings are directly relevant to PD, for which comparable strategies could guide the rational development of α-syn-targeted immunotherapies. While AD antibodies target extracellular Aβ aggregates, the pathology of PD primarily encompasses intracellular and conformationally diverse α-syn species: this creates substantial challenges with regard to epitope accessibility and antibody delivery (Davis et al., 2018). Several clinical programs illustrate both the potential and limitations of immunotherapy for PD. While cinpanemab (BIIB054) failed to achieve its primary endpoint in a Phase 2 trial, prasinezumab (RO7046015) modestly slowed down motor progression in specific subgroups, thus demonstrating mixed outcomes (Lang et al., 2022; Pagano et al., 2024; Wagner et al., 2013). Collectively, the mixed results regarding immunotherapy for PD and the extensive limitations of drug development for PD suggest that conventional strategies alone are unlikely to achieve meaningful disease modification, and that a more precise and mechanism-focused approach is warranted.

Development Trends for PD Drugs

Recent PD treatments are advancing as a result of improved understanding of disease pathophysiology and current therapeutic options. Recent trends in PD drug development focus on disease-modifying therapies, gene therapy, and AI/multiomics to identify novel therapeutic targets. Among the most promising research directions is the pursuit of disease-modifying treatments aimed at slowing or halting PD progression, rather than solely alleviating symptoms. Clinical trials on gene therapy have investigated delivery methods encoding neurotrophic factors or dopamine-synthesizing enzymes (LeWitt et al., 2011). Emerging biomarker technologies, particularly α-syn seed amplification assay (SAA), now enable in vivo detection of misfolded α-syn across genetic and idiopathic PD subtypes, including those previously thought to lack Lewy pathology (Kluge et al., 2024). For example, blood-based neuron-derived extracellular vesicle SAA demonstrated pathological seeding activity in approximately 60% of patients with Parkin-linked PD, challenging long-held assumptions about the absence of α-syn pathology in this genotype (Kluge et al., 2024). Similarly, SAA applied to plasma and CSF has shown high sensitivity for patients with prodromal and early PD, including those with rapid eye movement sleep behavior disorder and carriers of LRRK2/GBA mutations. These findings support its potential as a scalable diagnostic and enrichment tool for early-intervention trials (Yi et al., 2025). In parallel, targeting of α-syn condensation and aggregation dynamics, including phenolic small molecules that inhibit or disaggregate fibrils and peptides designed to modulate α-/β-syn interactions, is emerging as a disease-modifying strategy (Li et al., 2024; Yu et al., 2025a).

Advanced technological tools, including AI and multiomics, are increasingly integrated into PD research. AI enables the analysis of large-scale datasets to discover novel biomarkers, predict disease trajectories, and optimize treatment strategies (Belić et al., 2019). Multiomics (genomics, transcriptomics, proteomics, and metabolomics) data are utilized to elucidate complex molecular pathways underlying PD and identify novel drug targets (Chen et al., 2023). Combining these innovative approaches offers substantial promise for future PD treatment, particularly those targeting pathology, and improving patient outcomes.

LIMITATIONS OF DRUG DEVELOPMENT FOR PD

The development of therapeutics for degenerative brain diseases, including PD, AD, Huntington's disease, and amyotrophic lateral

sclerosis (ALS), encounters considerable challenges. These neurodegenerative disorders share key features, including progressive neuronal degeneration, abnormal protein aggregation, and limited therapeutic options that primarily address symptoms rather than underlying disease mechanisms. Despite extensive research efforts, numerous limitations impede the advancement of effective disease-modifying treatments.

Complexity of Disease Pathophysiology

A significant limitation in developing therapies for neurodegenerative diseases is the complexity and heterogeneity of the underlying pathophysiology. In PD, for instance, the loss of dopaminergic neurons in the substantia nigra is a well-established pathological hallmark, yet the precise cause of this neuronal degeneration remains uncertain (Obeso et al., 2017). Although oxidative stress, mitochondrial dysfunction, and protein aggregation (especially α-syn) are implicated in the disease process, the complex interactions among genetic predisposition, environmental exposures, and lifestyle factors complicate the understanding of PD pathogenesis (Schapira and Jenner, 2011). Similar challenges are observed in other neurodegenerative disorders, such as AD, wherein amyloid-beta plaques and tau neurofibrillary tangles are recognized pathological features, yet the underlying neuropathological mechanisms remain poorly defined (Selkoe and Hardy, 2016). Disease heterogeneity further complicates drug development. Patients with PD present with a broad spectrum of clinical manifestations and have varying disease progression rates and therapeutic responses, making the identification of universally effective therapeutic targets or biomarkers challenging (Athauda and Foltynie, 2015). Consequently, many drugs that show promise in preclinical studies fail in clinical trials, as they inadequately address the diverse biological mechanisms underlying disease progression.

Lack of Reliable Biomarkers for Early Diagnosis

Another obstacle in neurodegenerative disease drug development is the absence of reliable biomarkers for early diagnosis and disease progression monitoring (Shi et al., 2009). In PD, most patients receive a diagnosis only after extensive neuronal loss, significantly reducing the opportunity for interventions aimed at slowing disease progression (Berg et al., 2018). The lack of sensitive and specific biomarkers impairs the detection of diseases in their prodromal phases, complicating the initiation of treatments that might slow or halt progression. The use of CSF- and blood-based biomarkers, such as amyloid-beta and tau proteins, has demonstrated potential in the early diagnosis of AD but requires further investigation (Jack et al., 2018). Similarly, although research into PD biomarkers, including α-syn, is actively ongoing, no current single biomarker reliably enables early disease diagnosis or accurate prediction of disease progression (Yilmaz et al., 2019). Consequently, the absence of effective early diagnostic tools results in clinical trials predominantly enrolling patients with advanced disease, wherein the demonstration of disease-modifying effects is considerably more challenging.

Blood-Brain Barrier and Drug Delivery Limitation

The blood-brain barrier (BBB) is another substantial challenge in the development of therapeutics for neurodegenerative diseases. Although the BBB protects the brain from harmful substances in the bloodstream, the penetration ability of therapeutic compounds is limited (Abbott, 2013). Consequently, numerous promising drugs fail to achieve therapeutic concentrations in brain tissue because of insufficient permeability through the BBB. This limits the potential of small-molecule drugs and biologics, including monoclonal antibodies, whose large molecular sizes typically preclude effective BBB crossing (Pardridge, 2012). Multiple innovative strategies have been investigated to cross the BBB, such as nanoparticles, liposomes, and focused ultrasound-mediated transient disruption (Aryal et al., 2014). However, these techniques remain largely experimental and their long-term safety and clinical efficacy require comprehensive validation. Successfully overcoming the BBB remains a critical challenge in the development of effective neuroprotective therapies for PD and other neurodegenerative disorders.

Inadequate Preclinical Models

Another major challenge in neurodegenerative disease drug development is the inadequacy of current preclinical models to accurately replicate human pathology. Animal models, including rodent models of PD or AD, frequently under-represent the full complexity of human neurodegeneration, contributing to poor translational success in clinical trials (Dawson et al., 2010). For instance, most PD animal models rely on toxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or 6-hydroxydopamine, to induce dopaminergic neuron loss, but these models inadequately mimic the progressive nature of PD and largely overlook nonmotor symptomatology (McDowell and Chesselet, 2012). Likewise, animal models of AD, predominantly transgenic mice overexpressing amyloid-beta or tau, have resulted in numerous unsuccessful clinical trials due to their incomplete representation of human disease pathology (Drummond and Wisniewski, 2017). The fundamental disconnect between preclinical and clinical findings constitutes a significant barrier to successful therapeutic development, underscoring the need for predictive models that more accurately reflect human disease processes.

High Failure Rates in Clinical Trials

Despite substantial investments in research and development, drug development for neurodegenerative diseases faces exceptionally high failure rates. For PD, AD, and other neurodegenerative disorders, most therapeutics showing promise in preclinical studies fail in clinical trials (Cummings et al., 2021). Failure rates for PD and AD trials have been reported as high as 99%, with only a limited number of drugs achieving regulatory approval over the past 2 decades (McFarthing et al., 2024; Mullard, 2012). These frequent clinical disappointments stem from multiple factors, including poor translational predictability of animal models, incomplete understanding of underlying disease mechanisms, absence of reliable biomarkers, and significant challenges associated with drug delivery across the BBB. High costs and long time periods compound these

difficulties, discouraging continued investment in innovative treatments (Kola and Landis, 2004).

Economic and Regulatory Barriers

The economic and regulatory landscape significantly challenges neurodegenerative drug development. The prolonged timelines, high costs, and high failure rates associated with these diseases make it difficult for pharmaceutical companies to justify investing in new therapies, especially considering the limited market success of drugs approved for conditions like PD or AD (Arnerić et al., 2018; Conrado et al., 2020). Moreover, regulatory agencies, including the Food and Drug Administration in the United States and the European Medicines Agency, impose stringent requirements for demonstrating safety and efficacy, which can be especially difficult for neurodegenerative diseases, where biomarkers and clinical endpoints remain ill-defined (Stephenson et al., 2023). Initiatives like the Food and Drug Administration's Breakthrough Therapy and European Medicines Agency's PRIME intend to accelerate drug development, but they still lack clear guidance for neurodegenerative treatments (Vassar et al., 2009). Consequently, many potential therapies are delayed or abandoned due to the complex regulatory and financial challenges involved.

MULTIOMICS AND ARTIFICIAL INTELLIGENCE: DEFINITIONS AND RESEARCH TRENDS

Drug development for neurodegenerative diseases is being transformed by the integration of multiomics technologies and AI. These 2 distinct yet complementary approaches offer powerful tools for understanding the complex molecular landscapes of these diseases and identifying novel therapeutic targets.

Multiomics

Multiomics refers to the comprehensive analysis and integration of diverse "omics" datasets, including genomics, transcriptomics, proteomics, metabolomics, and epigenomics. This holistic approach enables researchers to study biological systems at multiple molecular levels, providing a more complete understanding of disease mechanisms (Hasin et al., 2017). The integration of various omics datasets has the potential to unravel the complexity of biological systems, as no single-omics layer can fully explain the intricate regulatory networks governing health and disease (Karczewski and Snyder, 2018). In neurodegenerative diseases, multiomics is leveraged to identify molecular signatures associated with disease onset, progression, and treatment response (Carrillo et al., 2025; Gu et al., 2023). Recent trends in multiomics research emphasize its application in personalized medicine and drug discovery. Multiomics enables patient stratification into molecular subtypes, facilitating targeted therapies (Vineis et al., 2020). By identifying specific molecular targets and pathways, multiomics helps researchers and clinicians develop more personalized approaches that hold promise for transforming the treatment landscape across diverse fields, including cardiology, oncology, and neurodegenerative diseases. Key methodological directions include single-cell and spatial multiomics, longitudinal profiling aligned to clinical phenotypes, and integration frameworks that improve molecular subtyping and response prediction (Yu et al., 2025b; Zou et al., 2025).

AI

AI refers to the development of computer systems using statistical learning, pattern recognition, and automated decision-making across diverse data types (Abiodun et al., 2019; (Guimerà Cuevas, 2024). In medical research, AI includes ML, DL, natural language processing, and artificial neural network techniques that enable the analysis of large and complex datasets. AI advancements are transforming medicine, enabling disease detection, imaging analysis, and personalized treatment (Topol, 2019). These trends stem from the ability of AI to analyze complex medical data, including imaging and electronic health records. DL enhances medical imaging by detecting disease-relevant patterns on MRI and computed tomography, including early AD-related hippocampal structural changes and atrophy linked to cognitive decline (Bron et al., 2015; Esteva et al., 2017; Litjens et al., 2017; Suk et al., 2017). Integration of imaging with genetic information can improve risk assessment and enable earlier, more precise diagnoses and timely interventions (Gaubert et al., 2021; Jack et al., 2013; Jo et al., 2019). Using DL-based feature extraction and pattern recognition, AI facilitates the generation of personalized diagnostic insights for PD and other neurological diseases. A significant trend in multiomics research is the use of AI to identify biological pathways and biomarkers (Zhao et al., 2025). For example, the Multi-Omics Factor Analysis framework is a method designed for the integrative analysis of multiomics (Argelaguet et al., 2018). It identifies latent factors that capture shared and modality-specific variation across different omics layers, enabling patient grouping and pathway association analyses. The integration of AI with multiomics is not only improving current diagnostic capabilities but also facilitating the shift toward more personalized, data-driven medical care, transforming the understanding and treatment of diseases like AD and cancer (Esteva et al., 2019).

Multiomics and AI Applications in PD

Recent research has begun integrating multiomics data using AI to better understand the complex mechanisms underlying PD. For example, Luo et al. (2025) developed a multiomics framework combining MRI-based radiomics, CSF biomarkers, and whole-genome sequencing analyzed through ML models to predict the progression of cognitive impairment in early PD (Luo et al., 2025). Their integrated model outperformed single-modality approaches, illustrating the value of cross-layer integration for PD trajectory prediction. The study highlighted how AI-driven multiomics integration can uncover cross-layer molecular and imaging signatures associated with PD pathophysiology. Tng et al. (2024) conducted a meta-analysis of 79 multiomics studies and identified 6 blood-based biomarker candidates for PD (eg, Arg1, SNCA, and APOA1) (Tng et al., 2024). Their findings demonstrated distinct molecular patterns associated with differential disease progression trajectories, enabling improved stratification of fast- and slow-progressing patients. Other studies utilized large-scale whole-blood RNA sequencing data to identify novel PD-associated RNAs, established a multiomics-

Table 1. Representative studies integrating AI and multiomics in PD research

Study	Multiomics modalities	AI/computational approach	Key findings
Luo et al. (2025)	MRI-based radiomics, CSF biomarkers, and whole-genome sequencing	Random Forest, Support Vector Machine, AdaBoost, Bayesian Classification, and Logistic Regression	Integrated model achieved accuracy 0.90 and AUC 0.928
Hu et al. (2024)	Whole-blood RNA sequencing	Support Vector Machine, Linear Regression, Logistic Regression, Stochastic Gradient Descent, AdaBoost, Gradient Boosting Classifier, Random Forest, K-Nearest Neighbors, and Multiple Layers Perception Classifier	Identified novel PD-associated RNAs and developed predictive diagnostic model
El Bouhaddani et al. (2024)	Transcriptomics, proteomics, and drug screening datasets	Probabilistic Orthogonal Partial Least Squares Discriminant Analysis	Identified HSPA5 as a candidate therapeutic target
Tng et al. (2024)	Blood-based proteomics and transcriptomics from multiomics literature	-	Identified 6 PD biomarker candidates and molecular signatures distinguishing fast- and slow-disease progression

AI, artificial intelligence; AUC, area under the curve; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PD, Parkinson's disease.

based ML model to predict PD diagnosis, thereby presenting a computational framework for biomarker development, early prediction, and patient stratification (Hu et al., 2024). In addition, a study integrating transcriptomic, proteomic, and drug screening data in synucleinopathy models related to PD discovered that *HSPA5* is one of the candidate genes that can be targeted for PD and synucleinopathy (El Bouhaddani et al., 2024). Such approaches not only enhance our understanding of disease heterogeneity but also provide a foundation for target identification, biomarker discovery, and precision drug development in PD research. Incorporation of similar frameworks into early-stage drug discovery studies may accelerate the identification of disease-modifying therapies and patient-specific treatment strategies. A summary of the recent studies applying AI and multiomics approaches in PD research, which are referenced in this section, is provided in Table 1.

OVERCOMING LIMITATIONS OF DRUG DEVELOPMENT USING AI AND MULTIOMICS

Despite persistent challenges in neurodegenerative drug development, the integration of AI and multiomics is transforming the research landscape. These technologies support biomarker-driven patient stratification and mechanism-aligned therapeutic design, thereby improving the strategic foundation for efforts toward the development of emerging PD therapies, including immunotherapy and personalized treatment.

First, the integration of AI and multiomics provides a deeper understanding of the complex pathophysiology of neurodegenerative diseases. A recent review emphasized interdisciplinary research using AI to integrate multiomics and clinical data for PD. These modules can aid diagnosis, prevention, and treatment validation (Yoon et al., 2024). Additionally, a recent study developed a platform utilizing imaging data from the nucleus, mitochondria, and ribosomes of neurons differentiated from human induced pluripotent stem cells of PD patients. This platform predicted PD subtypes, aiding patient-specific drug development (D'Sa et al., 2023). Another application in neurodegenerative diseases involved ALS, where researchers combined AI and multiomics to explore genetic and molecular variations across patient subgroups. The study integrated whole-genome sequencing, transcriptomic, and proteomic data from ALS patients to investigate disease heterogeneity (Chia et al., 2018). AI clustering and predictive modeling identified ALS molecular subtypes based on the expression of key genes, *SOD1* and *C9orf72* (Brown and Al-Chalabi, 2017). These subtypes were also characterized by differences in neuroinflammatory markers and oxidative stress pathways, as detected in proteomic profiles. These integrative analyses not only provided a deeper understanding of the molecular pathology of neurodegenerative diseases but also identified subtype-specific therapeutic targets, guiding personalized treatment approaches.

Second, the integration of AI and multiomics can be utilized to develop biomarkers for the early diagnosis of neurodegenerative diseases. For example, our recent study using proteomics identified 12 altered biomarkers in early AD plasma extracellular vesicles. Then, ML identified the optimal biomarker combination for early AD diagnosis based on the highest predictive success (Lee et al., 2024). Other researchers integrated genomic, proteomic, and metabolomic data from CSF samples of AD patients to identify early biomarkers of cognitive decline (Gulisano et al., 2018). An AI-driven analysis identified distinct proteomic signatures associated with early-stage AD, including changes in tau protein phosphorylation and amyloid-beta peptide levels (Kuhlmann et al., 2017). A study used a combination of genomic, proteomic, and lipidomic data from blood and CSF samples of patients with PD to investigate the biochemical changes linked to disease severity (Domingo and Klein, 2018). AI-based models revealed that mutations in genes such as *LRRK2* and *SNCA*, which are implicated in familial PD, were associated with specific changes in protein expression related to mitochondrial function and oxidative stress. Additionally, lipidomic data showed alterations in ceramide and phospholipid levels, which correlated with the rate of motor decline (Abbott et al., 2014). These multiomics frameworks are also increasingly being coupled with next-generation α-syn biomarkers to support precise patient

stratification and trial enrichment. By integrating α-syn SAA status with genetic, proteomic, and lipidomic signatures, multiomics approaches can define biologically coherent PD subtypes and enable biomarker-guided enrichment for disease-modifying trials (Kluge et al., 2024; Yi et al., 2025). AI complements this framework by detecting latent molecular patterns, identifying biomarkers, and uncovering diagnostic signatures that conventional analytical approaches may overlook. Together, AI and multiomics enable the development of predictive tools that can stratify patients based on their molecular profile, allowing for more personalized and effective interventions.

Third, by utilizing AI and multiomics, challenges associated with the BBB can potentially be overcome. One distinctive feature of CNS endothelial cells that preserves the isolated nature of the BBB is the abnormally low rate of vesicular transport (transcytosis). Lipidomic analyses have revealed that the lipid composition of CNS endothelial cells significantly differs from peripheral endothelial cells, with lipids transported by Mfsd2a suppressing caveolae vesicle formation, thereby maintaining BBB integrity (Andreone et al., 2017). Although little is known about which specific characteristics by which the BBB influences drug permeability, understanding its lipid composition could provide crucial insights for improving drug penetration. Additionally, AI-based approaches can predict and optimize the BBB permeability of novel drug candidates. In one study, an AI-driven "retro drug design" strategy generated 180,000 chemical structures capable of activating the μ-opioid receptor and penetrating the BBB. Among these, 25 compounds were identified as μ-opioid receptor agonists (Wang et al., 2022). Another study employed neural networks to design 26,581 small-molecule drugs capable of binding to dopamine D2 receptors and penetrating the BBB, with several demonstrating high BBB permeability and stability (Noori et al., 2024). These approaches can learn from data on molecular structures crossing the BBB and simulate interactions during drug transport. These simulations can propose structural modifications to enhance BBB permeability. Moreover, based on these insights, they will allow for the optimization of BBB permeability and the prediction of stability for these delivery methods.

Finally, AI and multiomics can be leveraged to support the development of PD drug including emerging PD immunotherapies. In therapeutic antibody development, epitope prioritization and Fc engineering are critical steps for achieving selective binding, optimizing effector function, and enhancing bioavailability (Brennan et al., 2025). Recent advances demonstrate how computational methods can accelerate these processes: eg, artificial neural network-based models have been used to predict peptide-binding affinities to major histocompatibility complex class I and II binding molecules and subsequently identify T-cell epitopes with potential immunogenicity (Reynisson et al., 2020). Similarly, support vector regression frameworks have been applied to predict Fc sequence combinations that maximize binding affinity and improve functional performance (Dumet et al., 2023). ML models have also been developed to predict absorption, distribution, metabolism, and excretion-related pharmacokinetic properties (Kosugi and Hosea, 2021), and their potential to inform half-life optimization strategies and guide antibody scaffold selection has been highlighted. Collectively, these examples illustrate how AI-enabled molecular design and in silico prediction can streamline immunotherapy development pipelines and support more rational and efficient engineering of biologics for PD.

AI and multiomics also provide a framework for more rigorous clinical evaluation of emerging PD therapies. A multimodal pharmacokinetic/pharmacodynamics approach (eg, linking longitudinal α-syn SAA measures and neuron-derived extracellular biomarkers with clinical scales and sensor-based digital readouts) may enable earlier assessment of target engagement and support predefined go/no-go decision rules (Caramia et al., 2018; Valerie et al., 2024). In parallel, adaptive, biomarker-anchored Phase 2 trial designs incorporating response-probability-based randomization and interim futility analyses could improve efficiency by prioritizing responsive subgroups and minimizing late-stage failures (Umbricht et al., 2024). Taken together, these strategies outline how computational and molecular tools may strengthen the translational pathway for future disease-modifying PD trials.

A translational workflow has been increasingly proposed to transform multiomics datasets into actionable therapeutic pipelines (Ahmadi et al., 2024; Sharma et al., 2024). Recent frameworks suggest that multiomics integration can be used to prioritize disease-relevant molecular networks and therapeutic targets by combining genetic causality, perturbation signatures, and protein-protein interaction topology (Dimitrakopoulos et al., 2018; Jiang et al., 2025; Ramos et al., 2024). AI-enabled screening tools such as DL models and molecular docking predictors further accelerate target identification by evaluating drug target interaction, drug-likeness, and BBB permeability in silico (Huang et al., 2024; Ren et al., 2023). Candidates are then validated in vitro, where transcriptomic or proteomic rescue signatures are assessed to determine whether the intervention restores disease-associated molecular pathways (Neuhoff et al., 2021). Candidates demonstrating pathway-level effects subsequently progress to animal studies followed by biomarker-anchored adaptive clinical trials to assess safety, target engagement, and disease-modifying potential (Budd Haeberlein et al., 2022; Leinenga et al., 2021). This trajectory illustrates how AI and multiomics shorten the bench-to-clinic transition by incorporating biological relevance, druggability, preclinical validation, and clinical decision-making guidelines into a single data-driven workflow. Although no PD therapy has yet advanced through this entire framework to receive approval, early-stage programs applying AI and multiomics-guided strategies reflect a growing shift toward rational, mechanism-based development pathways that may improve the probability of success for future disease-modifying trials.

CHALLENGES AND LIMITATIONS IN THE APPLICATION OF AI AND MULTIOMICS FOR PD DRUG DEVELOPMENT

Although the integration of AI and multiomics has demonstrated potential for identifying novel biomarkers and therapeutic targets for PD, several technical and translational challenges remain (Grenn et al., 2020; Schilder et al., 2022). From the omics perspective, heterogeneity across data types, nonstandardized preprocessing pipelines, and the lack of harmonized analytical

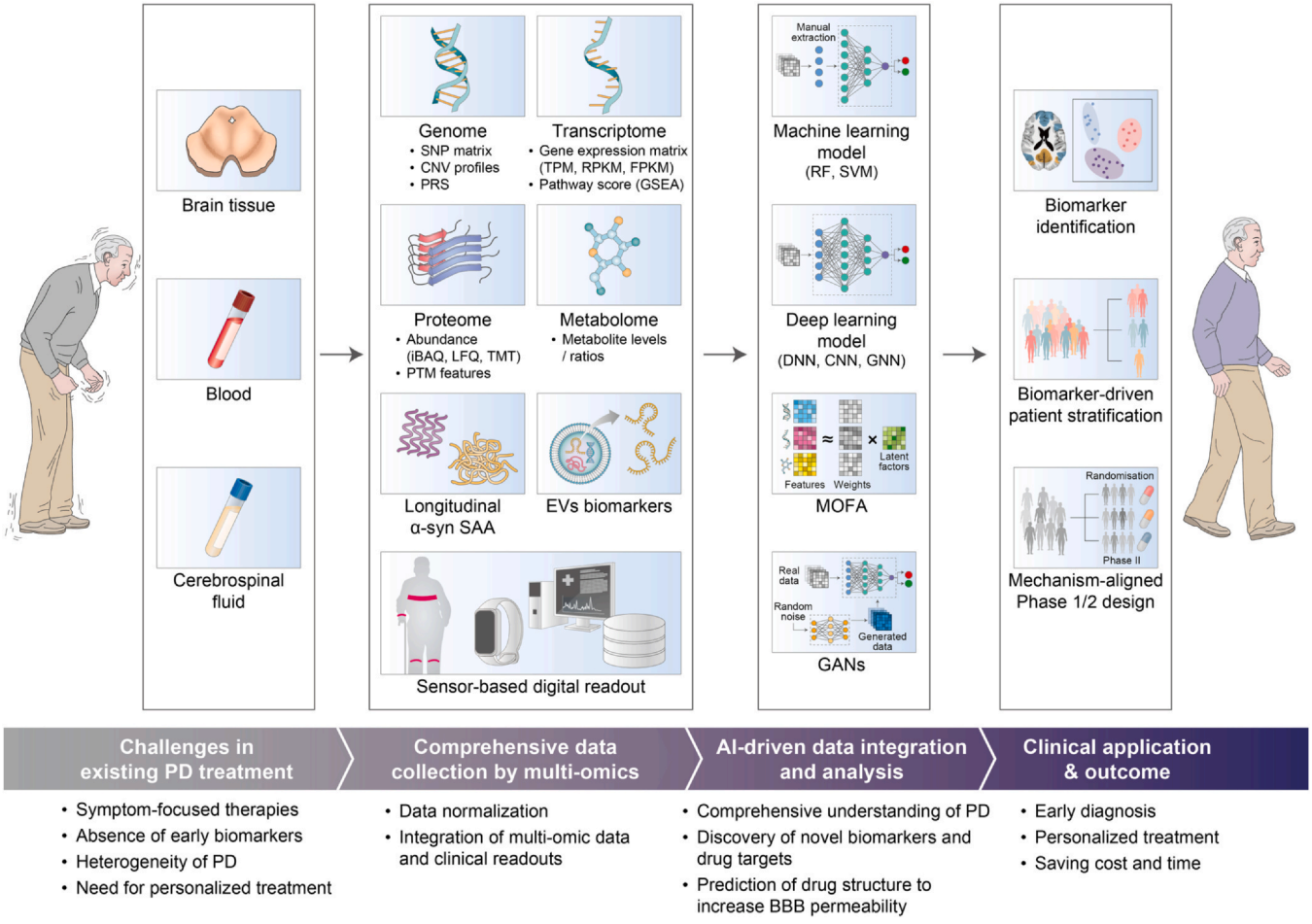

Fig. 1. Artificial intelligence (AI) and multiomics-driven drug development platform for Parkinson's disease (PD). The integration of multiomics data and AI for PD research. The workflow is divided into 4 key stages. In stage 1, traditional therapies focus primarily on alleviating symptoms without modifying disease progression. Limitations include the absence of early biomarkers, the complexity of PD, and the lack of personalized treatment options. In stage 2, comprehensive data are gathered from various "omics" layers, including genomics, transcriptomics, proteomics, and metabolomics, integrating longitudinal biomarker measurements with clinical readouts enables to capture a full molecular profile of PD. In stage 3, AI algorithms analyze multiomics data to identify early biomarkers, categorize patients into molecular subtypes, and discover new therapeutic targets. These insights facilitate more accurate diagnosis and the development of targeted treatments. In stage 4, insights derived from AI and multiomics integration lead to early diagnosis, personalized treatment plans, and accelerated drug discovery. This approach represents a shift from conventional methods to a precision medicine model that addresses the individual needs of PD patients. CNN, convolutional neural network; CNV, copy number variation; DNN, deep neural network; FPKM, fragment per kilobase of transcript per million mapped reads; GANs, generative adversarial networks; GNN, graph neural network; GSEA, gene set enrichment analysis; PRS, polygenic risk score; RF, random forest; RPKM, reads per kilobase per millions mapped reads; SNP, single-nucleotide polymorphism; SVM, support vector machine; TPM, transcripts per million.

frameworks often lead to inconsistent or irreproducible results (Schilder et al., 2022). The integration of genomics, transcriptomics, proteomics, and metabolomics requires substantial computational resources and robust statistical models to manage the inherent high dimensionality and noise in such data. Furthermore, the clinical interpretation of multilayered molecular interactions remains limited, emphasizing the need for validation in diverse patient populations (Coetzee et al., 2016; Schilder et al., 2022).

With regard to AI applications, DL and other ML approaches have shown superior accuracy in pattern recognition tasks (Marey et al., 2024; Miotto et al., 2018); however, their clinical translation faces critical barriers (Dinsdale et al., 2022; Eche et al., 2021). Model overfitting population bias, and limited generalizability across cohorts hinder the reliability of AI-assisted predictions (Dinsdale et al., 2022; Eche et al., 2021). Moreover, the "black-box" nature of many DL models restricts their interpretability, raising ethical and regulatory concerns regarding decision transparency and patient safety (Marey et al., 2024; Xu et al., 2022). As Dinsdale noted, even high-performing algorithms often fail to demonstrate tangible improvements in clinical outcomes: this underscores the so-called "AI chasm" between computational accuracy and real-world utility (Dinsdale et al., 2022; Xu et al., 2022).

In addition, privacy protection, and the integration of AI and multiomics outputs into electronic health records present

ongoing challenges for clinical implementation (Dinsdale et al., 2022; Miotto et al., 2018). Addressing these issues will require explainable AI frameworks, standardized data-sharing infrastructures, and large-scale prospective studies to ensure that these technologies contribute reliably and equitably to precision medicine for PD (Eche et al., 2021; Marey et al., 2024; Schilder et al., 2022).

CONCLUSION AND FUTURE PERSPECTIVES

Effective PD diagnostics and therapies must move beyond symptom-focused drugs like levodopa, which fail to halt progression and cause long-term complications (Ahlskog and Muenter, 2001). The lack of early biomarkers limits timely intervention, and the complexity of PD hinders personalized treatment development (Liu et al., 2025). A strategy integrating AI and multiomics integration is essential to address these limitations related to PD research and treatment challenges, and develop clinical applications. Therefore, such a suitable model of a personalized and data-driven platform is shown in Figure 1.

This platform integrates biological data with computational techniques for earlier diagnosis, targeted treatments, and accelerated drug discovery (Tan et al., 2021). Multiomics offers a comprehensive understanding of PD by integrating genomics, transcriptomics, proteomics, and metabolomics, to ascertain the molecular landscape and potential therapeutic targets of PD (Kodam et al., 2023). AI-driven analysis can pinpoint subtle molecular changes that serve as early indicators of PD (Sabherwal and Kaur, 2024), categorize patients into molecular subtypes based on unique profiles, and uncover pathways that traditional methods might overlook (Winklhofer and Haass, 2010). Indeed, AI-multiomics may overcome neurodegenerative drug challenges like BBB penetration and allow safer drug design (Andreone et al., 2017; Noori et al., 2024). Applying these advancements to PD could enable earlier diagnosis, individualized treatments, and identification of disease-modifying targets, fundamentally shifting PD management toward curative and preventive strategies. Leveraging AI and multiomics would overcome the current treatment limits, accelerate tailored therapy development, and improve patient outcomes.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Dayea Kim: Writing – original draft, Funding acquisition. **Eunji Cho:** Writing – review & editing, Conceptualization. **Hae-Un Jung:** Writing – review & editing, Writing – original draft. **Younghoon Go:** Conceptualization. **Parkyong Song:** Conceptualization. **Ye-Jin Kim:** Conceptualization. **Young Rae Ji:** Writing – original draft, Conceptualization. **Seulah Lee:** Writing – review & editing, Writing – original draft, Conceptualization. **Jaehoon Kim:** Writing – original draft, Conceptualization. **Yong-Seok Oh:** Conceptualization. **Jong Hyuk Yoon:** Writing – review & editing, Supervision, Conceptualization.

DECLARATION OF COMPETING INTEREST

None.

DATA AVAILABILITY STATEMENT

No datasets were generated or analyzed during the current study.

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