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ARTIFICIAL INTELLIGENCE AND PRECISION MEDICINE IN PARKINSON'S DISEASE: EMERGING DIAGNOSTIC AND THERAPEUTIC APPROACHES

Running Title: AI and Precision Medicine in Parkinson's Disease

Manisha[1], Soma Sekhar Pulamarasetti[1]*, Omkar Rai[1], Karan Gupta[1], Shivlal Yadav[2]

Author Details

Manisha[1]: Final Year B.Pharm Student, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh, India (458001). Email: manishapatidar0005@gmail.com

Soma Sekhar Pulamarasetti[1]*: Assistant Professor, Department of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh, India (458001). Email: dr.somasekhar@gmail.com | ORCID: 0009-0007-3552-1868

Omkar Rai[1]: Assistant Professor, Department of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh, India (458001). ORCID: 0009-0003-1861-3753

Karan Gupta[1]: Associate Professor, Department of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh, India (458001).

Shivlal Yadav[2]: Department of Pharmacy, Central University of Rajasthan, NH-8, Bandarsindri, Ajmer District, Rajasthan, Ind

Abstract:

Background: *Parkinson's disease (PD) is heterogeneous, both clinically, genetically and neuropathologically, which presents ongoing challenges for conventional syndromic clinical diagnostic criteria and uniform treatments. Recent advances in biofluid biomarkers, high-resolution neuroimaging and artificial intelligence (AI) have provided frameworks to reclassify PD on an objective biological basis and personalize therapeutic interventions 4 .*

Objective: *To critically synthesize recent advances in AI-driven diagnostic modalities, biological disease staging frameworks, biofluid biomarkers, genotype-targeted therapeutics and adaptive clinical trial designs in PD7.*

Data Sources: *A search was conducted in PubMed, MEDLINE, Scopus, Web of Science and other major biomedical literature databases for studies published mostly between 2018 and 20244.*

Review Methods: Evidence from clinical trials, neuroimaging studies, digital sensor evaluations, biofluid biomarker investigations, and regulatory science guidelines was reviewed using a comparative synthesis approach2 .

Key Findings: *The biological definition of PD, formalized by the Neuronal Alpha-Synuclein Disease Integrated Staging System (NSD-ISS), bases disease classification on in vivo seeded aggregation of alpha-synuclein () and dopaminergic neurodegeneration ()4. Deep learning models applied to single-photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) yield diagnostic classification accuracies in the range of 88%–99%5. Non-invasive digital devices such as radio-wave nocturnal breathing sensors and video-based kinetic software allow continuous surveillance at home6. Biomarker-enriched clinical trials8 are being driven by targeted therapeutics, including small-molecule and antisense oligonucleotide agents targeting LRRK2 and GBA1 mutations. But the implementation of these algorithms in practice is still held back by algorithmic overfitting, a lack of validation in diverse non-European cohorts and regulatory concerns around continuous machine learning updates13.*

Conclusion: *The combination of biological staging and AI-enabled digital phenotyping provides a scalable paradigm for early detection and targeted therapeutic selection in PD4. Standardized analytical pipelines, harmonized regulatory oversight , and adaptive clinical trial designs10 are needed for clinical translation.*

Keywords: *Parkinson Disease, Artificial Intelligence, Precision Medicine, Biomarkers, Machine Learning, Neurodegenerative Diseases*

Corresponding author:
Soma Sekhar Pulamarasetti,
Department of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh, India.
Mobile: +91-7095485741
Email Id: dr.somasekhar@gmail.com

QR CODE

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INTRODUCTION:

Parkinson's disease (PD) has traditionally been clinically defined and diagnosed by the presence of motor manifestations, specifically bradykinesia with resting tremor, rigidity or postural instability1. However, this clinical syndromic definition obscures the biological heterogeneity of the underlying neuropathology2. Progressive loss of dopaminergic neurons in the substantia nigra pars compacta and intraneuronal accumulation of misfolded alpha-synuclein (-syn) aggregates7 occur years before the appearance of overt clinical signs. Symptomatic therapies with levodopa and dopamine agonists do control motor symptoms, but do not impact the underlying neurodegeneration, primarily because interventions are applied uniformly across biologically different patient subgroups3.

The absence of validated progression biomarkers that could capture early pathological changes and stratify patients according to distinct molecular etiologies11 is a major hurdle to the development of disease-modifying therapies in PD. Cerebrospinal fluid (CSF) seed amplification assays (SAAs) and high-resolution neuroimaging have identified pathological anchors, but their integration into clinical practice and computational workflows is variable5. In addition, despite reports of high performance indicators in controlled diagnostic classification tasks, there are significant knowledge gaps regarding the generalizability to real-world clinical settings, alignment with emerging biological staging systems and compliance with regulatory structures for software oversight13.

This review critically examines the potential of the convergence of artificial intelligence, fluid and neuroimaging biomarkers, targeted molecular therapeutics and the current regulatory framework within the framework of PD precision medicine. The manuscript integrates the evidence for the Neuronal Alpha-Synuclein Disease Integrated Staging System (NSD-ISS) with deep learning architectures, non-invasive digital phenotyping, genotype-targeted pipelines (e.g., leucine-rich repeat kinase 2 inhibitors), and adaptive clinical trial methodologies to describe the translational pathways from biomarker discovery to regulatory compliance and patient care4.

Biological Reclassification and Staging by Biomarkers

Neuronal Alpha-Synuclein Disease Integrated Staging System (NSD-ISS)

Traditionally, the diagnosis of PD is based on the clinical motor signs, leading to the late therapeutic intervention when an estimated 50% to 70% of nigrostriatal dopaminergic neurons have already degenerated 15 . To circumvent this limitation, the Neuronal Alpha-Synuclein Disease Integrated Staging System (NSD-ISS) redefines PD biologically4. In this framework, disease definition is based on objective biological anchors independent of clinical presentation: pathological neuronal α-synuclein aggregation referred to as "α-synucleinopathy" (detected by biofluid seed amplification assays) and dopaminergic neuronal dysfunction referred to as "dopaminergic deficit" (quantified by dopamine transporter [DAT] single-photon emission computed tomography [SPECT] or positron emission tomography [PET])7. Genetic risk factors (pathogenic variants in LRRK2 or GBA1) are indicated as "11.

The NSD-ISS classifies individuals on a biological continuum from Stages 0 to 67. Stage 0 is defined as individuals who are fully asymptomatic with pathogenic genetic alterations () before biomarker positivity7. Stage 1 necessitates biomarker positivity for pathological -synuclein () in the absence of dopaminergic dysfunction or clinical symptoms7. Stage 2 is a prodromal stage defined by status, with or without dopaminergic dysfunction (or) and is characterized by subtle clinical signs or non-motor symptoms (e.g., hyposmia, REM sleep behavior disorder [iRBD], or subtle cognitive changes) that do not cause functional impairment7. Stages 3-6 describe progressive functional impairment from mild motor or non-motor dysfunction to severe disability requiring total dependence2.

Operational strengths and complexities of the NSD-ISS2 have been highlighted in recent cross-sectional evaluations of established cohorts, including the BioFIND cohort and the Systemic Synuclein Sampling Study (S4). Most of the (BioFIND) participants (96.3%) in the BioFIND study of moderately advanced PD met biological criteria with CSF Syn-SAA, and most participants were in Stage 32. When NSD-ISS criteria were applied to medicated cohorts, however, there was significant overlap in Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III motor scores within Stages 3 and 42. Symptomatic dopaminergic medications also are known to affect motor severity scores, so patients with advanced disease may score in mild functional brackets, making stage assignment complicated11. This points out the need of objective drug independent progression biomarkers besides functional scales11.

SynNeurGe research criteria, in addition to the NSD-ISS, propose a three-part classification according to Synuclein pathology (), Neurodegeneration () and Genetics ()1. While NSD-ISS limits itself to neuronal synucleinopathies (excluding oligodendroglial pathology such as multiple system atrophy), SynNeurGe offers a wider perspective for differential diagnosis in atypical parkinsonian syndromes1. Application of these

biological frameworks to clinical research provides a structured baseline to improve patient accrual in disease-modifying clinical trials4.

Biofluid Biomarkers and Seed Amplification Assays

The creation of seed amplification assays (SAAs), such as Real-Time Quaking-Induced Conversion (RT-QuIC) and Protein Misfolding Cyclic Amplification (PMCA), has been a step forward in the diagnosis of neurodegenerative diseases4. These assays take advantage of the self-propagating nature of pathological -synuclein seeds to induce misfolding of recombinant monomeric -synuclein substrates, amplifying femtogram amounts of aggregates into detectable fluorescent signals7. 2 Syn-SAA has overall sensitivities from 87 to 95% and specificities higher than 95% in CSF samples for differentiating idiopathic PD from healthy controls.

Although CSF diagnostic sensitivity is high, lumbar punctures are invasive, which limits routine longitudinal monitoring12. Translational research has therefore focused on identifying peripheral blood-based biomarkers12. Total -synuclein quantification in unfractionated plasma suffers from inconsistent diagnostic utility due to the high concentrations from red blood cells where peripheral hemolysis adds analytical noise12. To overcome peripheral dilution, the focus has been shifted to neuron-derived extracellular vesicles (EVs) isolated from plasma using cell-surface markers including L1CAM12. Pathological -synuclein species such as phosphorylated serine-129 (-) and oligomeric forms enriched in neuronal EVs correlate better with central disease processes than whole plasma12.

In parallel, non-synuclein fluid markers provide complementary information on neuroaxonal loss and neuroinflammation30. The neurofilament light chain (NfL) measured on ultra-sensitive single-molecule array (Simoa) platforms is a quantitative index of axonal degeneration 30 . In typical PD, plasma NfL levels are only moderately increased compared to healthy age-matched controls, but markedly higher NfL concentrations are found in atypical parkinsonian disorders, such as progressive supranuclear palsy (PSP) and multiple system atrophy (MSA)30. Plasma NfL is therefore an important biomarker for differential diagnosis30 . In addition, Glial Fibrillary Acidic Protein (GFAP) is a marker of activation of astrocytes and higher levels are associated with cognitive decline in PD cohorts31. Integrated multi-omics workflows have also identified blood transcriptomic signatures such as the synergistic expression pair AP3B1 and BMPR2, offering non-invasive multi-biomarker options for early detection27.

AI Frameworks for Diagnostic and Prognostic Stratification

Deep learning architecture for neuroimaging

Artificial intelligence, in particular deep learning (DL), offers automated techniques for analyzing complex neuroimaging modalities5. Single-photon emission computed tomography (SPECT) using iodine-123-ioflupane (, commonly called DaTscan) quantifies the density of dopamine transporters in the striatum5. Visual interpretation of DaTscans by nuclear medicine specialists is successful in identifying significant reductions of striatal binding but early or mild asymmetric losses in the putamen are susceptible to inter-observer variability5. Feature representations of striatal uptake are automatically extracted by Convolutional Neural Networks (CNNs) trained on 2D and 3D SPECT projections5. Architectures with residual connections, dense feature fusion (e.g., DenseNet and ResNeXt) and spatial attention mechanisms achieve classification accuracies between 88% and 99% for PD vs. healthy controls using datasets from the Parkinson's Progression Markers Initiative (PPMI)5.

High field strength structural magnetic resonance imaging (MRI) at 3T and 7T yields high-resolution anatomical detail5. Advanced sequences provide sub-millimeter structural features15 such as Quantitative Susceptibility Mapping (QSM) for measurement of nigral iron deposition and T2*-weighted imaging for loss of nigrosome-1 (the "swallow-tail" sign). Deep transfer learning architectures (e.g., VGG16, InceptionV3 and EfficientNetB0 in combination with gradient-boosted decision tree algorithms such as XGBoost) are used to analyze structural MRI data to identify subtle midbrain atrophy and iron accumulation14. Overall classification accuracies >94% on validated benchmark cohorts5 have been achieved by these hybrid networks.

Although diagnostic performance is high in the scientific literature, its translation into clinical workflows has important limitations19. Models trained on curated, highly homogenous research repositories (e.g. PPMI) often suffer degraded performance when deployed on heterogeneous clinical scans that are impacted by variations in hardware manufacturers, acquisition protocols, slice thicknesses, and motion artifacts19. High standalone predictive accuracy in binary classification tasks (PD vs. Healthy Controls) does not reflect the clinical reality, where the main difficulty lies in discriminating early PD from atypical parkinsonian syndromes23. To address these translational hurdles, deep learning models need to be trained on multi-center clinical cohorts with diverse disease controls and explainable AI techniques (for example, Gradient-weighted Class Activation Mapping [Grad-CAM]) that directly link algorithm decisions to recognizable anatomical

structures5.

Digital Biomarkers & Non-Invasive Contactless Sensing

Besides central imaging and biofluids, AI-powered digital phenotyping tools offer scalable means for continuous and non-invasive disease monitoring9. Traditional clinical assessments (e.g., MDS-UPDRS) are based on episodic in-clinic evaluations that only capture a single timepoint of symptom severity, and mask diurnal fluctuations, medication "off" states and white-coat effects3.

One interesting advance in contactless digital assessment is the tracking of breathing patterns during the nite using radio-wave sensing6. Yang et al.6 used an attention-based neural network to train an AI model to extract respiratory chest movements from low-power radiofrequency signals reflected off a sleeping individual. Evaluation of this platform in >7,600 individuals showed an area under the receiver operating characteristic curve (AUC) of 0.90 for internal test sets and 0.85 for external validation cohorts for detection of PD6. Moreover, the model predicted overall motor severity and longitudinal disease progression in line with MDS-UPDRS total scores (), demonstrating that passive home-based sensing can track disease trajectories without patient burden6.

Complementary computer vision and audio algorithms assess motor dysfunction from short video and sound recordings16. For instance, the PARK tool (Parkinson's Analysis with Remote Kinetic-tasks) employs lightweight deep learning frameworks (e.g., UFNet) for analyzing webcam recordings of standardized motor tasks such as rapid finger tapping, facial expressions, and vocalizations16. These systems extract fine-grained spatial-temporal features to identify subclinical kinetic degradation and vocal dysarthria16. Such digital biomarkers are continuous, objective data streams that can enhance clinical trials by detecting treatment responses earlier than episodic manual rating scales3.

Computational Multimodal Integration and Clinical Toolkits

Single diagnostic modalities such as biofluid assays, structural neuroimaging or digital motion metrics have limited ability to capture isolated facets of PD pathophysiology12. A crucial component of precision medicine approaches is computational multimodal integration of heterogeneous data streams into unified machine learning frameworks20.

Combining CSF or plasma biomarker concentrations with SPECT striatal binding ratios, QSM iron density metrics and sensor-derived gait parameters in ensemble deep learning models results in improved diagnostic sensitivity and prognostic accuracy over individual models5. Multimodal cross-attention networks learn complex non-linear correlations between disparate datasets, allowing for early identification of distinct phenotypic subtypes (e.g. diffuse-malignant versus tremor-dominant slowly progressive variants) in the disease course3. The integration of these predictive algorithms into clinical decision support systems gives clinicians access to a dynamic risk profile that enables the selection of individualized therapies and enrichment for clinical trials9.

Targeted Molecular Interventions and Precision Therapeutics

Genotype-Specific Drug Discovery: LRRK2 and GBA Subtypes

Advances in understanding disease-associated genetic variants 8 are driving the shift toward precision therapeutics in PD. Mutations in LRRK2 (leucine-rich repeat kinase 2) and GBA1 (glucocerebrosidase) are two of the most common genetic causes of familial and sporadic PD8.

Autosomal dominant mutations in LRRK2, most notably the substitution, cause hyperactivation of LRRK2 kinase activity8. This hyperactivation leads to impaired autophagic-lysosomal clearance, defective endosomal trafficking, and accumulation of pathological α-synuclein8. Small-molecule LRRK2 kinase inhibitors (such as BIIB122/DNL151) and antisense oligonucleotides (ASOs, such as BIIB094/ION859) targeting LRRK2 mRNA for RNase H-mediated degradation are in Phase 1 and Phase 2 clinical trials8 . These specific treatments are designed to normalize kinase activity, reduce the accumulation of toxic substrates, and slow the progression of disease in both LRRK2 mutation carriers and subset populations of sporadic PD with elevated LRRK2 pathway activation8.

Mutations in GBA1 lead to deficiency of the lysosomal enzyme glucocerebrosidase (GCase), causing accumulation of the substrates glucosylceramide and glucosylsphingosine18. This accumulation destabilizes physiological α-synuclein tetramers and favors the formation of toxic oligomers29. Therapeutic approaches for GBA1-associated PD include small-molecule chaperone therapies that stabilize misfolded GCase enzymes, substrate reduction therapies that reduce glycolipid burdens, and adeno-associated virus (AAV)-mediated gene replacement therapies that seek to deliver functional copies of GBA1 directly to the central nervous system18.

Target Identification and Mitophagy Modulation Using AI

Genotype-specific approaches, combined with artificial intelligence platforms, accelerate small-molecule drug discovery by modeling structural biology and predicting drug-target interactions18.

Machine learning algorithms screen large virtual compound libraries against complex protein structures to identify molecules that can modulate specific pathological cascades 18 .

A prominent example of AI-driven drug discovery in PD is the discovery of small molecules that reestablish mitophagy, i.e., the selective autophagic removal of damaged mitochondria38. Mitochondrial dysfunction and oxidative stress are the major pathologic features in both sporadic and familial PD25. Researchers used machine learning screening models to identify that probucol, an agent that lowers lipids, can promote mitophagy38. In animal models (including Drosophila and zebrafish), activation of mitophagy by probucol prevented dopaminergic neuronal loss and improved motor function after mitochondrial insult38.

In addition, computational platforms assist in elucidating endolysosomal degradation pathways and neuroprotective peptides38. For instance, exercise-induced peptides, like irisin, promote the clearance of pathological α-synuclein preformed fibrils through endolysosomal processing, thus protecting neurons from aggregate-induced toxicity38. The integration of AI target identification platforms with high-content cell imaging accelerates the translation of candidate compounds from in silico discovery to preclinical validation18.

Adaptive Clinical Trial Methods and Translational Regulatory Science

Precision Trial Architectures: Protocols & Bayesian Modifications

Traditional trial designs, i.e. fixed-sample, long-duration randomized controlled trials with clinically heterogeneous patient populations without biological stratification3, are partly to blame for the historical failure rate of neuroprotective clinical trials in PD. Modern precision medicine demands new trial designs that can evaluate targeted treatments in enriched patient populations10.

Master protocols, like umbrella, basket and platform trials, offer flexible frameworks for precision medicine10. Umbrella trials test several targeted candidate therapies simultaneously, within a single disease entity, assigning patients to specific treatment arms based on specific molecular biomarkers (e.g., matching LRRK2 carriers with LRRK2 inhibitors, and GBA1 carriers with GCase chaperones)10. Basket trials evaluate one targeted intervention across multiple disparate diseases that share a common biomarker or genetic mutation10. Platform trials are run continuously, permitting early termination of unpromising intervention arms for futility, and the addition of new candidate therapies to the infrastructure over time10.

Bayesian response-adaptive designs for clinical trials18 are intertwined with master protocols. As opposed to frequentist trial designs that require fixed sample sizes and static interim analyzes, Bayesian adaptive designs update probability distributions continuously as patient data accrue.32 Response-adaptive randomization increases the probability of assignment of newly enrolled participants to therapeutic arms with evidence of interim efficacy, while interim sample size re-estimation allows dynamic adjustment of the target for recruitment10. We reduce the required sample sizes and trial durations by using stage-resolved biological markers (e.g., changes in SAA quantitative parameters, plasma NfL trajectory slopes, or digital motor features) as surrogate endpoints in Bayesian models18.

Regulatory Science, SaMD Frameworks and Good Machine Learning Practices

Regulations set by global bodies, including the U.S., need to be followed to successfully translate artificial intelligence algorithms and digital healthcare technologies into cleared software products. Food and Drug Administration (FDA) and the European Medicines Agency (EMA)9. Algorithms designed to diagnose, monitor or predict PD progression fall within the regulatory classification of Software as a Medical Device (SaMD)13.

In response to the difficulties presented by adaptive, machine learning-based software, regulatory agencies have published a set of guiding principles, known as the Good Machine Learning Practice (GMLP)13. Traditional regulation of medical devices assumes static hardware or frozen software code13. Yet, sophisticated AI models, especially those that learn continuously13, might alter the feature weights underlying the model as new data is presented. GMLP frameworks require strict adherence to protocols throughout the software development lifecycle, including dataset segregation (ensuring training data is kept completely separate from validation and testing sets), minimizing algorithmic bias across sex, age, and ethnicity subgroups, and Predetermined Change Control Plans (PCCPs)13. PCCPs establish the limits of allowable algorithmic change in the post-market setting, enabling software enhancements while maintaining safety and efficacy, without necessitating new regulatory submissions for incremental changes13.

Clinical deployment of digital biomarkers at multiple sites also requires analytical validation (demonstrating that the sensor accurately measures the physiological parameter), clinical validation (showing that the measured parameter correlates with PD severity or clinical state) and usability across various patient populations13. Transparent

and reproducible data pipelines according to GMLP guidelines are essential for regulatory approval and clinical implementation of AI-driven diagnostic tools13.

Structures Comparative Analyzes

In an effort to compare the diagnostic technologies and precision therapeutic frameworks presented, the following tables summarize key performance indicators, limitations in practice and levels of clinical implementation.

Table 1: Comparison of AI-Based Diagnostic and Monitoring Modalities in Parkinson's Disease

Modality	Extracted Feature / Signal	Deep Learning Architecture	Diagnostic Metric (Accuracy / AUC)	Primary Operational Limitations
DaTscan SPECT Imaging	Striatal dopamine transporter binding density and putaminal binding asymmetry	3D Convolutional Neural Networks (CNNs), DenseNet, ResNeXt	Accuracy: 88.9% – 100% AUC: > 0.98	High cost, radiation exposure, limited availability in primary care, poor differentiation of early atypical parkinsonism

Table 2: Stratification of Precision Therapeutics Across Biological NSD-ISS Stages

Biological Target / Gene	Pathological Pathway	Precision Agent Class	NSD-ISS Target Stage	Clinical Trial Phase & Status	Key Biomarker Endpoint
***LRRK2* Kinase**	Hyperactivation, endolysosomal trafficking arrest, α-syn clearance failure[8]	Small-Molecule Kinase Inhibitor (BIIB122)[8]	Stage 2B to Stage 3 ($S+, D+$)[7]	Phase 2 Active[8]	Reduction in urine Rab10 phosphorylation, stabilization of CSF α Syn seeds[8]
***LRRK2* mRNA**	Overexpression of mutated transcript[17]	Antisense Oligonucleotide (BIIB094 / ION859)[17]	Stage 2B to Stage 4 ($S+, D+$)[7]	Phase 1/2 Completed/Active[17]	CSF LRRK2 protein reduction, safety/tolerability metrics[17]
***GBA1* / GCase**	Glucocerebrosidase enzyme deficiency, glycolipid substrate accumulation[18]	AAV9 Gene Augmentation Therapy / Small Molecule Chaperones[18]	Stage 1 to Stage 3 ($G+, S+$)[7]	Phase 1/2 Active[18]	Leucocyte GCase activity restoration, plasma glucosylsphingosine reduction[18]
Mitophagy / Mitochondria	Impaired clearance of damaged mitochondria, ROS generation[25]	Mitophagy Enhancers (AI-Screened Probucol)[38]	Stage 2A to Stage 3 ($S+$)[7]	Preclinical / Translational Proof-of-Concept[38]	Mitochondrial membrane potential restoration, ROS normalization[38]

Neuronal α-Synuclein Seeds	Toxic oligomer formation, template propagation[7]	Seed Aggregation Inhibitors / Monoclonal Antibodies[3]	Stage 1 to Stage 2 ($S+$ Pre-motor/Prodromal)[7]	Phase 2 Continuous Evaluation[3]	Reduction in CSF αSyn-SAA maximum fluorescence (F_{max}) and latency time extension[7]

DISCUSSION:

Parkinson's disease management is transitioning from a clinical, symptom management approach to a precision medicine approach, based on biological staging and AI-driven diagnostics4. The development of biological criteria, as the NSD-ISS and SynNeurGe frameworks, moves PD to objective pathological anchors (, , and) instead of only motor syndromes4. This structural change solves a major problem in neurodegenerative drug discovery: that biologically heterogeneous groups have been recruited into clinical trials, causing the failure of previous disease-modifying candidates10.

At the same time, artificial intelligence provides diagnostic toolkits for the analysis of high-dimensional biological data5. High performance in diagnostic classification has been demonstrated by deep learning models trained on SPECT and MRI data5. However, one important finding from the evaluation of these models is that high diagnostic accuracy on benchmark datasets (e.g., PPMI) does not automatically guaranty clinical utility19. In real-world clinical settings, models are challenged by hardware variations, motion artifacts, and overlapping symptoms from atypical parkinsonian syndromes.19 Thus, AI models should be developed from independent binary classifiers into interpretability-oriented multi-class decision support systems integrated directly into biological staging workflows5.Additionally, fluid and neuroimaging biomarkers, as well as non-invasive digital phenotyping (e.g., radio-wave nocturnal breathing sensors, webcam-based kinetic software) allow for continuous, real-world monitoring.6 These tools can detect subtle functional differences not measured by periodic in-clinic assessments, providing sensitive digital endpoints for clinical trials3. These platforms, coupled with genotype-directed therapeutics (e.g., small molecule LRRK2 inhibitors, ASOs) and adaptive clinical trial designs (e.g., Bayesian platform trials) offer a comprehensive pipeline for precision drug development8.Regulation demands that use of AI tools in routine practice follows the Good Machine Learning Practice (GMLP) and Software as a Medical Device (SaMD) guidelines13 . Regulatory oversight should balance model stability and adaptivity, using Predetermined Change Control Plans (PCCPs) to safely manage software updates 13. Algorithmic fairness in demographic subgroups and standardized reference materials for biofluid assays are required for equitable, global implementation12.Future Directions

The future of precision medicine for Parkinson's disease will be multi-omic fusion models integrating genomic, transcriptomic, epigenomic and proteomic data with continuous digital streams20. With the development of ultra-sensitive assay platforms, peripheral biofluid detection, in particular EV profiling of neurons in plasma, will likely approach analytical parity with CSF seed amplification assays, thus reducing the need for invasive lumbar punctures12.

10. The use of master protocols and adaptive Bayesian trial designs will become the norm for early phase interventional studies in therapeutic development The synergy of AI-based virtual screening, disease modeling with patient-derived induced pluripotent stem cell (iPSC) and biomarker enriched enrollment will facilitate the candidate selection process and clinical validation18. In addition, the integration of passive, contactless home monitoring in clinical trial protocols will enable real-time monitoring of disease velocity and treatment response, thereby accelerating the creation of targeted, disease-modifying therapies for PD6.
Research Gaps 2.1.
But technological advances do not yet fill up all the major research gaps in diagnostic, therapeutic and computational areas:

Longitudinal validation of biological staging: Large prospective population-based cohorts are needed to determine transition rates between stages and to evaluate staging performance in medicated patients2.
Harmonized peripheral biofluid assays: Standardized reference materials and analytical protocols are needed for plasma synuclein assays and neuronal EV isolation to reduce inter-laboratory variability and blood cell contamination12.Algorithmic Generalizability and Bias. Deep learning models are mostly trained on homogeneous, high-quality research datasets that represent a small fraction of the population, with

little or no validation on heterogeneous clinical data from underrepresented populations.16
Mechanistic Integration of Digital Biomarkers Further mapping of the physiological mechanisms underlying the association between non-motor digital features (e.g. subtle changes in nocturnal breathing architecture) and specific regional neurodegenerative processes is needed6.Continuous Learning Regulatory Systems: There are incomplete standardized regulatory pathways for post-market surveillance of adaptive, continuous-learning artificial intelligence algorithms in clinical practice13. Clinical Considerations
Biological staging and precision tools based on AI have direct implications for clinical practice:
Move to Early Biological Diagnosis Neurodegenerative pathology can be diagnosed by clinicians in the prodromal or pre-symptomatic stages ( ) thus allowing neuroprotective interventions to be used before significant nigrostriatal depletion4.

Targeted Therapeutic Choice Molecular subtyping allows for genotype-specific treatment, with patients with LRRK2 or GBA1 mutations being placed on targeted treatments rather than non-specific dopaminergic agents8.
Objective Continuous Evaluation: Non-invasive digital sensors in home care allow for objective monitoring of disease progression and response to medication, shifting away from episodic clinical assessments6.Improved differential diagnosis: Complex algorithms based on deep learning applied to structural MRI and DaTscans may assist in differentiating early PD from atypical parkinsonism, minimizing the risk of diagnostic errors5. Limits of the Existing Evidence

The results of this review should be interpreted in light of methodological limitations in the literature to date:
Cohort Heterogeneity: Many neuroimaging and biomarker studies report use of datasets (e.g. PPMI or BioFIND) that have stringent inclusion criteria and may not represent the multi-comorbid clinical population2.Cross-sectional study designs: Many AI algorithm validations are cross-sectional and therefore conclusions about predictive capacity for long-term clinical trajectories are limited.19

Dopaminergic Medications Produce Confounding Effects Symptomatic motor treatments alter clinical rating scale scores and introduce confounding variables when staging systems and digital sensors are validated in medicated cohorts2.
Publication Bias : Reported diagnostic accuracies for proprietary or novel deep learning models may be high because only positive performance indicators are selectively published 19 .
Abstract The management of Parkinson’s disease is being transformed by the integration of artificial intelligence, fluid and neuroimaging biomarkers, targeted molecular therapeutics, and modern regulatory systems. Biological models such as the NSD-ISS reframe PD, shifting the diagnostic focus from late motor signs to early pathological mechanisms4. Advanced deep learning architectures and contactless digital phenotyping platforms provide non-invasive approaches for early detection, patient stratification and continuous longitudinal tracking.5 These technologies, coupled with adaptive clinical trial designs, provide the opportunity to evaluate genotype-directed therapies. However, to translate these advances into routine healthcare, further validation at multiple centers, standardization of assay standards, transparent AI models and regulatory compliance under the Good Machine Learning Practice guidelines12 are required. Availability of data and materials
No new datasets were generated or analyzed for this article, so data sharing is not applicable. All data used in this review are from published literature cited in the text.

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