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Toward Personalized Medicine in Parkinson's Disease: A Scoping Review of Biomarkers, Genetics, and Treatment Stratification

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ABSTRACT

Personalized medicine is transforming Parkinson's disease (PD) care by tailoring therapies to patients' genetic, biomarker, and clinical profiles. Given PD's heterogeneity, this strategy offers new possibilities for disease-modifying interventions beyond symptom management. A systematic search of PubMed and EBSCO MegaFILE was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines. Studies addressed genetic profiling, biomarker discovery, individualized therapeutic strategies, or experimental/computational models relevant to personalized PD care. Twenty studies were included. Major themes identified were the use of genetic markers such as *LRRK2* and *GBA* mutations for patient stratification; advances in alpha-synuclein and other biomarkers for early diagnosis, though standardization remains a barrier; the application of patient-derived induced pluripotent stem cell (iPSC) models and brain organoids to test genotype-specific therapies; and the integration of multi-omics and machine learning to refine disease subtyping and drug discovery. Challenges included limited access to genetic testing, a lack of validated biomarkers, and barriers to clinical translation. Personalized medicine in PD is progressing rapidly, but significant barriers remain before it can be fully integrated into routine care. Future priorities include validating biomarkers, expanding pharmacogenetic infrastructure, and translating biologically informed strategies into clinical practice.

Keywords: Biomarkers, genetics, Parkinson's disease, personalized medicine, stratification.

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INTRODUCTION

Personalized medicine is revolutionizing healthcare by offering personalized approaches tailored to the unique genetic, environmental, and lifestyle characteristics of individuals.[1] This shift is particularly important in Parkinson's disease (PD), as it is a heterogeneous disorder with wide variability in symptoms, progression, and treatment responses.[2] Current treatment strategies for PD primarily focus on symptom management rather than modifying disease progression.[3] While dopamine replacement therapies such as levodopa provide significant symptom relief, they fail to address the underlying neurodegenerative processes that drive disease worsening over time.[4] This highlights the urgent need for more targeted therapies that can modify the disease course, not just manage symptoms.

Recent discoveries in genetic profiling and biomarker research have brought the promise of personalized medicine within reach for PD patients.[5] Genetic mutations, such as those in the *LRRK2* gene (particularly the G2019S mutation), play a crucial role in both familial and sporadic forms of PD.[6] Understanding how these genetic mutations contribute to disease pathogenesis opens the door to more targeted therapeutic strategies.[6] Additionally, alpha-synuclein, a protein that forms toxic aggregates in the brains of PD patients, has emerged as one of the most prominent biomarkers in the study of PD.[7] Its presence and misfolding are defining features of the disease, and its measurement in cerebrospinal fluid (CSF), blood, and even salivary glands holds significant promise for early detection and disease monitoring.[7]

Integrating genetic profiling and biomarkers into clinical practice continues to pose significant challenges. Although these discoveries have advanced understanding of the mechanisms underlying PD, translating them into effective therapeutic strategies remains complex. The potential of biomarker-guided therapeutic strategies depends on stratifying patients according to their genetic makeup, disease severity, and response to therapy.[8] Treatment stratification, which means matching the right therapies to the right patients, is at the forefront of personalized care in PD. However, it remains underexplored in clinical practice.[9] Furthermore, genetic testing, biomarker validation, and targeted therapies still face significant barriers, including cost, accessibility, and the need for further validation in large, diverse populations.[10]

Despite these challenges, the field of personalized medicine in PD is rapidly evolving. For example, clinical trials targeting the *LRRK2* mutation, which affects a subset of individuals with PD, have shown promising results and highlight the potential for disease-modifying therapies.[11] Similarly, alpha-synuclein-based therapeutics, including vaccines and small molecules designed to prevent its aggregation, are in various stages of development.[12] These treatments represent an intersection between research and clinical care, and biomarker-guided interventions may soon transition from the laboratory to practice, offering more personalized options.

This scoping review aims to examine the evolving field of personalized medicine in PD, with particular emphasis on biomarkers, genetics, and treatment stratification. Drawing on evidence from clinical trials, experimental disease models, and computational research, it explores how mutation-targeted therapies, patient-derived stem cell technologies, and multi-omics integration are reshaping the foundations of personalized PD care. The review also assesses emerging diagnostic frameworks and pharmacogenetic tools that support more tailored clinical decision-making. By mapping these developments, it highlights both the scientific advances enabling personalized strategies and the persistent barriers, such as limited biomarker validation and obstacles to clinical translation. Ultimately, this review offers a comprehensive overview of current innovations and outlines key priorities for integrating personalized medicine into routine PD management.

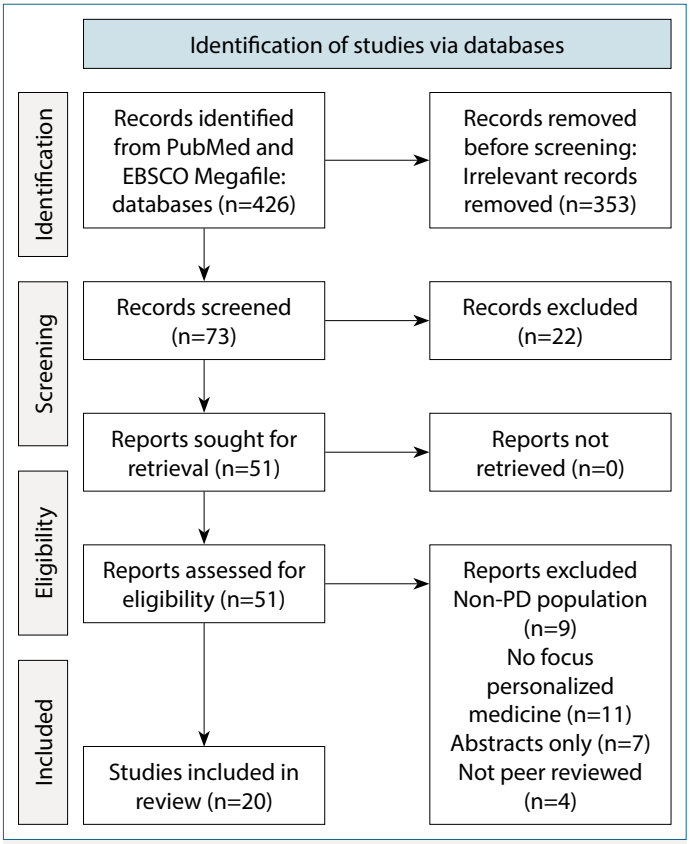

Figure 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram for systematic search.

This scoping review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[13] A systematic literature search on biomarkers, genetics, and treatment stratification was performed using PubMed and the EBSCO MegaFILE electronic databases, supplemented by manual searches (Fig. 1). The databases were searched from inception to April 11, 2025, and results were restricted to articles published in English. A detailed list of search terms is provided in Appendix 1.

Studies were included if they met the following criteria: involved individuals diagnosed with PD; focused on personalized medicine or personalized/stratified treatment

Table 1. Inclusion and exclusion criteria for the scoping review

Parameter	Inclusion criteria	Exclusion criteria
Population	Studies involving individuals diagnosed with PD.	Studies involving individuals diagnosed with atypical parkinsonism.
Exposure	Studies including at least one of the following: genetic profiling (e.g., *LRRK2*, *SNCA*, *GBA1*), biomarkers (e.g., alpha-synuclein), treatment response stratification, individualized therapeutic strategies, or experimental/computational models relevant to personalized PD care.	Studies not including any form of genetic profiling, biomarkers, or treatment stratification related to PD.
Focus	Studies on personalized medicine in PD, focusing on genetic profiling, biomarkers, treatment response stratification, individualized therapeutic strategies, or preclinical models contributing to personalized strategies.	Studies not related to personalized medicine or that do not address genetic profiling, biomarkers, treatment stratification, or personalized treatment strategies.
Study design	Original research or reviews.	Editorials, letters, commentaries, or conference abstracts.
Language and publication	Studies that are peer-reviewed and published in English.	Studies that are not peer-reviewed, published in languages other than English, or without full-text availability.

strategies; included at least one of the following: genetic profiling (e.g., *LRRK2*, *SNCA*, *GBA1*), biomarkers (e.g., alpha-synuclein), treatment response stratification, individualized therapeutic strategies, or experimental/computational models relevant to personalized PD care; were original research or reviews; were peer-reviewed; and were published in English. Studies were excluded if they focused on atypical parkinsonism (e.g., multiple system atrophy, progressive supranuclear palsy) without reference to PD; did not address personalized medicine; did not include genetic profiling, biomarkers, or treatment stratification related to PD; were editorials, letters, commentaries, or conference abstracts; were not peer-reviewed; were not published in English; or lacked full-text availability (Table 1).

CLINICAL AND RESEARCH CONSEQUENCES

Genetic Stratification and Mutation-Directed Therapies

A consistent theme across the included studies was the growing use of genetic profiling to guide treatment strategies and disease modeling in PD. Several articles focused on specific mutations, particularly in *GBA1* and *LRRK2*, which are among the most well-established genetic contributors to familial and early-onset PD. Collectively, these studies emphasized that pharmacological interventions should be adapted to individual molecular characteristics rather than relying solely on observable clinical features (Table 2).

In 2020, Mullin et al.[14] conducted a non-randomized, open-label trial exploring the effects of ambroxol, a pharmacological chaperone, in people with and without *GBA1* mutations. The study showed that ambroxol was able to cross the blood-brain barrier, increase glucocerebrosidase (GCase) activity, and affect α-synuclein levels, which are key markers in *GBA*-associated PD. While clinical improvements were limited, this study provided important proof-of-concept evidence that lysosomal dysfunction can be targeted in genetically stratified patients.

That same year, Schneider and Alcalay published a review highlighting advances in mutation-directed therapies, including *LRRK2* kinase inhibitors and enzyme replacement therapies for *GBA* mutations. They acknowledged significant progress in understanding the biological mechanisms of these mutations but also noted major barriers, such as difficulties recruiting sufficient numbers of genetically defined participants and limited generalizability due to the low frequency of these mutations in the broader PD population.[15]

In a follow-up review, the same authors pointed to a growing trend of clinical trials using genotype-based inclusion criteria. They described ongoing studies of compounds such as venglustat, a glucosylceramide synthase inhibitor, and ambroxol as examples of a shift toward biology-based interventions. Importantly, they argued that genetic stratification reduces heterogeneity within clinical trial populations, making it easier to determine whether an intervention is effective.[16]

However, not all authors were equally optimistic. In another 2020 review, von Linstow et al.[17] offered a more cautious

Table 2. Summary of included studies

Authors	What was studied
Džoljić et al. (2015)[28]	Pharmacogenetics; genetic influences on individual response to Parkinson's disease (PD) medications
Korczyn and Hassin-Baer (2015)[32]	Personalized medicine approaches to modify disease progression in PD
Xu et al. (2016)[23]	Induced pluripotent stem cell (iPSC) models for PD; treatment and disease modeling
Kalinderi et al. (2016)[30]	Genetic background of PD; monogenic and risk gene associations
Lee et al. (2017)[25]	3D brain organoids using iPSCs for modeling PD and neurodegenerative disorders
Ferreira and Massano (2017)[29]	Review of genetic mutations and clinicopathological correlations in PD
O'Hara et al. (2018)[26]	Disease-modifying therapies targeting α-synuclein aggregation
Mullin et al. (2020)[14]	Drug repurposing; ambroxol therapy targeting *GBA1* mutations and α-synuclein
Whiffin et al. (2020)[19]	Genetic loss-of-function variants in *LRRK2* and implications for therapy
von Linstow et al. (2020)[17]	Personalized medicine; evaluation of *GBA*- and *LRRK2*-targeted trials
Schneider et al. (2020)[16]	Targeted therapeutics for *GBA*, *LRRK2*, *SNCA*-related PD
Schneider and Alcalay (2020)[15]	Personalized medicine; genetics-based treatments (*GBA*, *LRRK2*)
Chu et al. (2021)[18]	Genetic profiles; implications for clinical practice and ethnic differences in PD
La Cognata et al. (2021)[20]	Multi-omics; stratified medicine using genomics, transcriptomics, proteomics
Katta et al. (2023)[24]	Advanced molecular therapies, including gene editing, gene silencing, and stem cell therapy for PD
Liu et al. (2022)[22]	Computational drug repurposing using random walk and supervised learning
Thanprasertsuk et al. (2023)[33]	Genetic profiling; *GBA* mutations and levodopa-induced dyskinesia
Höglinger and Lang (2024)[31]	Frameworks for biological classification of PD using genetics and biomarkers
Chen et al. (2024)[21]	Computational; machine learning-assisted genetic prioritization for drug discovery
Balestrino et al. (2024)[27]	Device-assisted therapies in PD with genetic mutations (*GBA*, *SNCA*, etc.)

perspective. While they acknowledged the promise of *GBA*- and *LRRK2*-targeted therapies, they questioned how applicable these approaches are to idiopathic PD, where such mutations may act more as modifiers than primary causes. Their review highlighted the ongoing need to define the boundaries of mutation-specific strategies and determine how broadly they can be applied.

In a complementary line of research, another group of investigators reviewed the frequency of *LRRK2* mutations in East Asian populations and supported the inclusion of ethnicity-informed genetic screening to help identify at-risk individuals. Their findings suggested that personalized medicine strategies should be adapted regionally, particularly in populations where certain mutations are more prevalent.[18]

Lastly, Whiffin et al.[19] conducted a large-scale genomic analysis examining the safety of targeting *LRRK2*. Their study found that individuals with naturally occurring loss-of-function (LoF) variants in *LRRK2* did not experience significant adverse health effects. These findings support the safety profile of partial *LRRK2* inhibition, which is an important consideration for the continued development and clinical approval of targeted therapies.

Computational Tools and Multi-Omics Integration

Another important topic in the included studies was the use of computational tools and multi-omics strategies to better define PD subtypes and improve treatment selection. These approaches reflect a broader shift from generalized, symptom-based care toward more individualized, data-driven strategies (Table 2).

A review by La Cognata et al.[20] emphasized the value of integrating different "omics" layers, such as genomics, transcriptomics, proteomics, and metabolomics. According to the authors, studies relying on only one of these data types often miss critical connections between genes and downstream biological processes. They discussed several examples where multi-omics approaches enabled the identification of molecular subtypes with distinct treatment response profiles. These findings point toward a future in which more precise biomarkers can guide personalized treatment decisions.

In 2024, a group of investigators introduced a machine learning model called ML-GPS (Machine Learning-assisted Genetic Priority Score), designed to enhance drug target discovery across 112 chronic diseases by integrating genetic associations from both rare and common variants. Rather than

identifying entirely novel targets, ML-GPS helped prioritize known candidates more systematically by providing stronger genetic support. For example, although *LRRK2* had already been recognized as a PD target, ML-GPS strengthened its relevance and ranked it among the top-scoring candidates. The model broadened the range of potential targets compared to traditional strategies, improving sensitivity and specificity while offering more biologically plausible drug leads. This illustrates how artificial intelligence can refine and accelerate drug discovery in complex diseases like PD.[21]

Similarly, Liu et al.[22] developed a hybrid model combining protein-protein interaction networks with supervised machine learning to uncover new drug-disease associations. Their model highlighted connections involving key PD-related proteins such as α-synuclein and tau, and its predictive performance (area under the curve [AUC]=0.827) demonstrated strong potential for drug repurposing. These computational frameworks illustrate how bioinformatics can accelerate both the development and personalization of PD treatments.

Experimental Models for Personalized Interventions

Several included studies focused on developing laboratory models that replicate the genetic and cellular features of PD, particularly for testing personalized therapies. These experimental models are critical for bridging the gap between genetic discoveries and individualized treatment plans (Table 2).

Xu et al.[23] provided a comprehensive overview of induced pluripotent stem cell-derived (iPSC-derived) dopaminergic neuron models created from patients carrying mutations in *PARK2*, *PINK1*, *LRRK2*, and *SNCA*. These models were able to reproduce central features of PD, including mitochondrial dysfunction, oxidative stress, and α-synuclein accumulation. The authors noted technical barriers such as variability in differentiation efficiency but concluded that iPSCs provide a scalable, patient-specific platform for testing targeted therapies.

Building on this, another group of investigators explored the use of clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) gene-editing in iPSC models, particularly to study *SNCA* mutations. They demonstrated how gene editing can be applied either to correct mutations in patient-derived cells or to introduce them into control lines, enabling direct comparisons. This approach offered insight into mutation-specific disease mechanisms and raised the possibility of gene-based therapeutic interventions. However, concerns such as genome stability and immunogenicity remain important considerations.[24]

Lee et al.[25] extended these advances by developing 3D brain organoids from human pluripotent stem cells. These "mini-brains" mimicked key structural and functional aspects of the midbrain and provided a more physiologically relevant environment for drug testing. The organoids enabled high-throughput screening and were used to assess dopaminergic function and synaptic integrity, making them a promising next-generation tool for evaluating therapies that target specific genetic mutations.

Disease-Modifying Strategies and Pharmacogenomics

A primary objective of personalized medicine is to move beyond symptom management and slow or even halt disease progression. Several included studies addressed this goal by exploring disease-modifying therapies and pharmacogenetically informed treatment planning (Table 2).

A 2018 review focused on therapies targeting α-synuclein, including monoclonal antibodies, small molecules, and GCase-enhancing agents. The authors highlighted that treatment success often depends on timing, baseline biomarker levels, and the extent of α-synuclein pathology. They emphasized the need for trials designed around biological subtypes, noting that earlier failed trials may have been limited by a lack of stratification.[26]

Another study examined the use of levodopa-carbidopa intestinal gel (LCIG) in a group of patients with known genetic mutations. Those with *GBA1* mutations experienced greater motor improvement, although cognitive effects remained a concern. Based on these findings, the authors recommended personalized treatment protocols that consider both motor and non-motor outcomes.[27]

Some researchers focused more on pharmacogenomics. They analyzed how gene variants in *COMT*, *MAOB*, and *DRD2* influence treatment response and the risk of side effects, such as levodopa-induced dyskinesia. The review suggested that tailoring drug regimens to genetic profiles could reduce complications and improve adherence. However, the authors also noted that pharmacogenetic testing is not yet widely adopted in clinical settings, marking a gap between research and practice.[28]

Two broader reviews proposed reframing PD not as a single disease but as a spectrum of biologically distinct subtypes. They argued that defining PD in molecular terms, rather than purely by symptoms, can improve the segmentation of clinical trials and support more personalized therapeutic approaches.[29,30]

Biomarker-Based Diagnostic and Classification Frameworks

For personalized medicine in PD to be effective in practice, it requires robust, biologically informed tools for diagnosis and patient stratification. Several studies addressed this need by proposing new diagnostic models based on pathophysiological markers (Table 2).

Höglinger and Lang introduced a framework called SynNeurGe, which incorporates genetic risk factors, imaging biomarkers, and α-synuclein pathology. Their goal was to improve early identification of patients most likely to benefit from targeted treatments. The authors emphasized that traditional symptom-based classifications often blur distinctions between synucleinopathies and fail to capture underlying biological mechanisms.[31]

Similarly, Korczyn and Hassin-Baer[32] advocated for a classification system based on pathophysiology, such as mitochondrial dysfunction, lysosomal impairment, or inflammation, rather than symptoms alone. They argued that this pathway-oriented approach would enable earlier, and more personalized intervention strategies.

Supporting these frameworks, one study found that patients with *GBA* mutations and early-onset PD had a significantly higher risk of developing levodopa-induced dyskinesia. This type of genetic insight has practical implications not only for predicting treatment outcomes but also for informing preventive care decisions and long-term management strategies.[33]

CONCLUSION

Advancing Genetic Stratification in Clinical Research

The studies included in this review highlight the growing role of genetic stratification in shaping the future of personalized medicine for PD. Mutations in genes such as *GBA* and *LRRK2* consistently emerged as key targets for research and clinical trials. Investigations of *GBA1*-targeted therapies such as ambroxol, along with *LRRK2* inhibitor development, suggest that tailoring treatment based on genetic subtypes may lead to more precise and effective interventions. Stratifying patients by genotype is also helping to improve the design and efficiency of clinical trials, offering a more focused approach than broad symptom-based recruitment.

However, while the potential of genetic stratification is compelling, several uncertainties remain. One major issue is the variable expression of these mutations in real-world patients, particularly in sporadic PD, where many individuals do not carry known pathogenic mutations or where the significance of identified variants remains unclear.[34] Even among those with high-penetrance mutations, disease onset and progression can vary considerably, indicating that other modifiers, such as genetic, environmental, or epigenetic, are also involved.[34] To move genetic stratification from theory into routine clinical care, a deeper understanding of these complex genotype-phenotype relationships across diverse populations is needed.

Opportunities and Limitations of Experimental Disease Models

Many studies included in this review emphasized the value of advanced disease models for exploring the biological mechanisms of PD and testing personalized treatment strategies. Technologies such as patient-derived iPSCs, CRISPR/Cas9 gene editing, and 3D brain organoids provide powerful platforms to simulate disease at the cellular level. These models replicate hallmark features of PD, such as mitochondrial dysfunction and α-synuclein aggregation, and enable controlled testing of genotype-specific therapies.[35]

This strategy is essential for studying rare familial mutations, where traditional models and population-level studies may be insufficient.[35] That said, most of these technologies are still in preclinical or proof-of-concept stages. Issues such as standardization, cost, and the long-term functional reliability of these models need to be addressed before they can be widely used in clinical decision-making.[35] Similar critiques have been raised in reviews of disease modeling for other neurodegenerative conditions, where variability in differentiation outcomes and concerns over genomic stability remain unresolved.[36] These models hold great promise, but further validation is needed to ensure they can reliably inform patient care.

Multi-Omics and Machine Learning in Drug Discovery

The integration of computational tools and multi-omics analyses was also emphasized in many studies included in this review. Machine learning and genetic prioritization models have been applied to identify drug targets, define biologically relevant subgroups, and better understand the relationships between genes and disease pathways. These data-driven methods have the potential to significantly improve how treatments are discovered, developed, and delivered.[37]

Yet translating this potential into clinical impact is still a work in progress. High-quality, annotated datasets are critical for developing reliable algorithms, but such resources are not consistently available across research settings. Differences in omics platforms, inconsistencies in bioinformatics pipelines, and the absence of clinical interpretation standards all pose challenges. Although the reviewed studies demonstrate what is possible with computational biology, they also underscore a clear gap between model development and clinical application. Closing this gap will require collaborative efforts to develop validated, interoperable frameworks that can be integrated into clinical workflows at scale.

Toward a Biologically-Based Classification of Parkinson's Disease

Several studies advocated for redefining PD, shifting from a purely clinical syndrome to one understood through biological classification. Frameworks such as SynNeurGe and

models focused on pathway-specific stratification propose categorizing patients by genetic mutations, molecular biomarkers, and core pathophysiological features such as mitochondrial dysfunction or neuroinflammation.[31] These approaches could improve diagnostic accuracy, streamline trial enrollment, and increase the likelihood of matching patients with effective, disease-modifying therapies.

This direction mirrors the evolution seen in oncology, where biomarker-based treatment selection has become standard practice.[38] In PD, however, widespread adoption of biology-based classification is still limited. One of the main barriers is the availability of clinically validated biomarkers. Although genomics, proteomics, and imaging have advanced, few biomarkers have been incorporated into diagnostic criteria. For example, cerebrospinal fluid (CSF) alpha-synuclein measurement is not yet standardized or widely used to guide treatment.[7] As other reviews have noted, this lack of biomarker infrastructure continues to slow the clinical translation of biologically informed models.[8]

Translational Barriers and Systemic Challenges

Despite clear scientific advances, the studies included in this review also highlight practical barriers that must be addressed before personalized medicine becomes a standard part of PD care. One such barrier is that only a small proportion of PD patients carry actionable genetic mutations, which limits the scalability of mutation-specific interventions.[6] Furthermore, routine access to genetic and pharmacogenetic testing is still lacking in many healthcare settings, creating a barrier to personalized care at the point of diagnosis and treatment.[10]

Other implementation gaps include the absence of clinical decision-support tools and limited training for providers on how to interpret and apply genetic information. These issues are compounded by the early-stage nature of many interventions described in the literature. For example, while the Phase II trial of prasinezumab provided valuable baseline data, it also underscored the need for longer-term follow-up to evaluate real-world efficacy and safety.[39] Without robust longitudinal evidence, it will be difficult for these innovative approaches to gain traction in routine clinical practice. Building a practical infrastructure to support personalized medicine in PD will require coordinated investments in research, education, and policy.

Implications for Future Research and Practice

As biomarker validation progresses and genetic testing becomes more accessible, personalized approaches to PD care are likely to increasingly influence treatment guidelines and clinical trial design. Future clinical research should focus on standardizing omics-based diagnostics, developing decision-support tools for clinicians, and ensuring equitable access to stratified therapies. Integrating these innovations into routine care will require not only scientific breakthroughs but also regulatory, educational, and infrastructural support.

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Appendix 1. Search terms

("Parkinson Disease" or "Parkinson's Disease") and ("Personalized Medicine" or "Precision Medicine" or "Individualized Therapy" or "Stratified Medicine") and ("Biomarkers" or "biomarker" or "Alpha-Synuclein" or "Alpha Synuclein" or "*LRRK2*" or "*GBA1*" or "*SNCA*" or "*PINK1*" or "Parkin") and ("Genetic Testing" or "Genomics" or "Genetic Predisposition to Disease" or "Gene Mutations") and ("Treatment Outcome" or "Therapy" or "Disease Management" or "Treatment Response" or "Clinical Implementation").