# Metabolomics in Parkinson's disease biomarker discovery and drug evaluation study

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**Abstract:** Metabolomics, as a tool for systematically studying metabolites in biological systems, has become a key approach in exploring the pathogenesis of Parkinson's disease (PD) and evaluating drug efficacy. This article, based on the latest metabolomics research, discusses the discovery process of PD biomarkers, the analysis of related metabolic pathways, and strategies for evaluating drug efficacy. By analyzing the metabolic differences between healthy and PD groups, several key biomarkers were identified, and their potential in PD diagnosis and treatment was explored. Additionally, the combination of metabolomics with organ-on-chip technology provides a new avenue for drug safety evaluation. This study offers important theoretical insights for the early diagnosis of PD and drug evaluation.

## 1 Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder globally, affecting approximately 0.3% of the population, with prevalence increasing significantly with age [1]. Prevalence rises to 1% in individuals over 60 and reaches 4% in those over 80, indicating that aging is a significant risk factor for PD development. The primary clinical manifestations of PD include bradykinesia, postural instability, muscle rigidity, along with cognitive impairments, attention deficits, and executive dysfunction. Additionally, patients often experience sleep disorders, which significantly diminish their quality of life.

PD imposes significant physical and mental burdens on patients while also profoundly impacting their families and society. Patients often become incapacitated, diminishing their ability to care for themselves, which places caregiving responsibilities on family members, thereby disrupting their work and daily life. Moreover, the growing number of PD patients is driving up healthcare costs, intensifying the pressure on the public health system.

Current clinical treatments for PD primarily involve pharmacotherapy, surgery, and physical rehabilitation, with drug therapy being the most commonly used approach. Levodopa remains the most effective treatment for PD, alleviating motor symptoms by replenishing dopamine levels in the brain. However, prolonged Levodopa use often leads to complications such as motor fluctuations and dyskinesia. To mitigate these effects, dopamine agonists are commonly administered alongside Levodopa. For patients unresponsive to medication, deep brain stimulation (DBS) is considered the most effective surgical intervention, where electrodes are implanted to stimulate specific brain regions and alleviate motor symptoms. Physical rehabilitation is also essential for maintaining and improving motor function while reducing complications due to functional decline. Speech therapy, in particular, plays a crucial role in managing speech disorders and dysphagia.

Despite the effectiveness of current treatments in alleviating symptoms, the pathogenesis of PD remains incompletely understood, limiting the development of therapeutic strategies targeting the disease's underlying causes. Research indicates that PD's pathologic process involves multiple complex factors, including mitochondrial dysfunction, oxidative stress, and disruptions in protein metabolism (Figure 1). Impaired mitochondria and excessive reactive oxygen species (ROS) damage neurons, leading to cell death. Furthermore, the accumulation of α-synuclein due to defective protein metabolism is a pathological hallmark of PD, where misfolded α-synuclein forms Lewy bodies, ultimately triggering neuronal death. Inflammation and immune responses are also critical in PD pathogenesis. Studies have demonstrated that neuroinflammatory responses are prevalent in the brains of PD patients, with microglia-released inflammatory factors exacerbating neuronal damage, highlighting the significant role of inflammation in the disease. Additionally, dysregulated calcium homeostasis, genetic mutations, and hereditary factors may contribute to the onset of PD [2].

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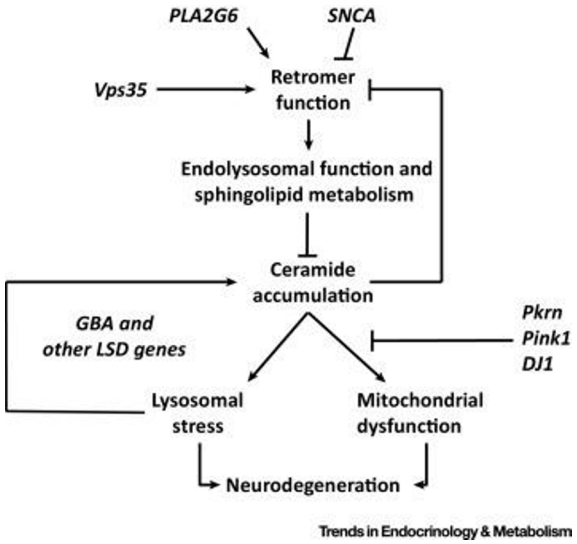


**Figure 1.** Possible pathogenesis of PD.

Given the widespread dangers of PD and the insufficiency of existing treatments, the search for new therapeutic strategies has become a major focus of scientific research. Metabolomics, a field that qualitatively and quantitatively analyzes all small-molecule metabolites in biological systems, offers new insights into PD research. By examining the dynamic changes of metabolites in living organisms, metabolomics can uncover the metabolic signatures of PD at various pathological stages, providing a scientific foundation for early diagnosis, monitoring disease progression, and facilitating personalized treatment approaches. Currently, the primary methods used in metabolomics include nuclear magnetic resonance (NMR) and liquid chromatography-mass spectrometry (LC-MS). Of these, LC-MS has become the most widely adopted due to its high sensitivity and reproducibility [3].

The application of metabolomics in PD research, particularly in biomarker discovery and metabolic pathway analysis, has shown considerable advantages (Figure 2). Through the comprehensive analysis of metabolite alterations, untargeted metabolomics can identify potential metabolic profiles during the early or preclinical stages of PD, thus enabling the possibility of early diagnosis. Additionally, metabolomics facilitates personalized treatment by identifying metabolites linked to disease states and drug responses. This allows for the prediction of patient responses to various treatment regimens, providing data to support the adjustment of therapies and drug dosages. Moreover, metabolomics serves as a valuable tool for monitoring PD progression, offering dynamic insights into the metabolic status of patients and enabling more accurate assessment of disease advancement.

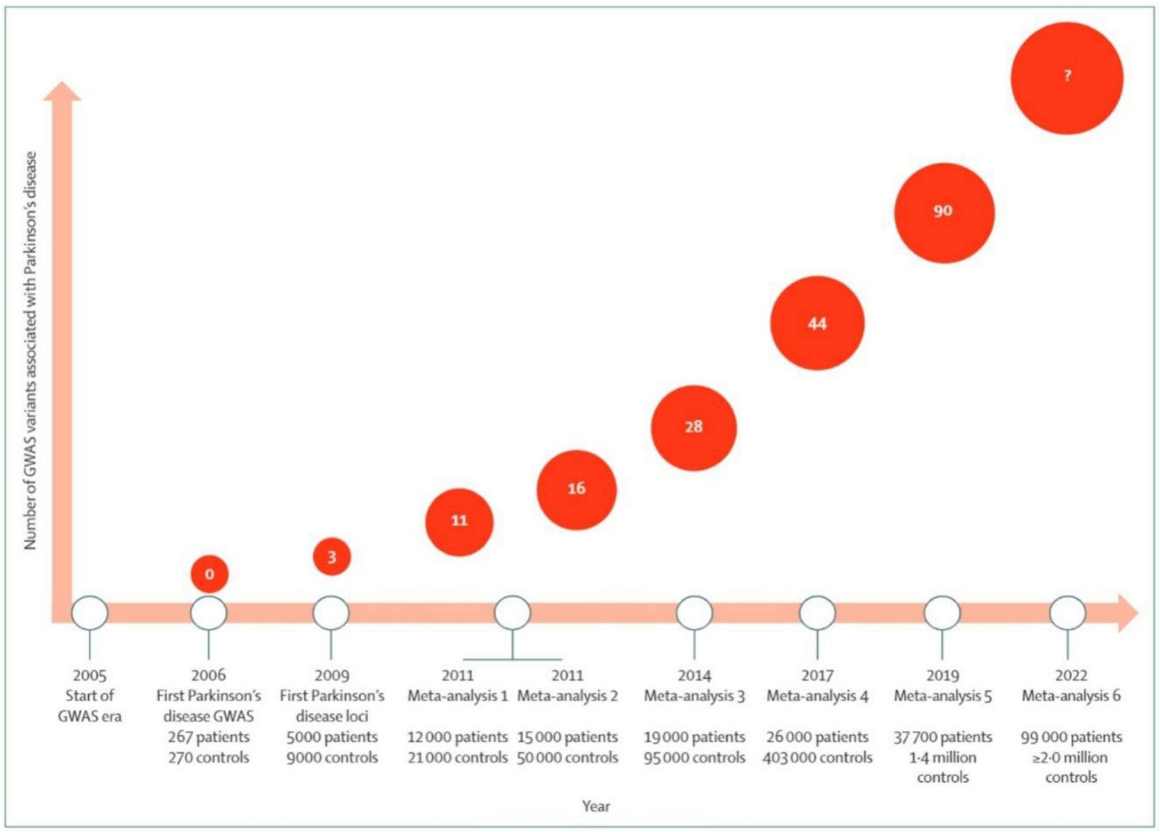


**Figure 2.** Timeline of Parkinson's disease gene discovery in genome-wide association studies.

The aim of this study is to investigate the effects of PD on endogenous metabolites and its pharmacotherapeutic mechanisms through metabolomics, thereby providing a foundation for the identification of new therapeutic targets and the development of more effective treatment strategies.

## 2 Metabolomics in Parkinson's disease research

### 2.1 Biomarker discovery

Biomarkers are biomolecules that indicate disease states or drug responses, playing a crucial role in the early diagnosis and personalized treatment of diseases. Early diagnosis of Parkinson's disease has long been a significant challenge, but the advent of metabolomics offers a promising solution. By comprehensively analyzing metabolites in a patient's blood, urine, or cerebrospinal fluid, metabolomics can identify biomarkers that are strongly associated with the disease, thereby laying the foundation for early diagnosis (Figures 3, 4).

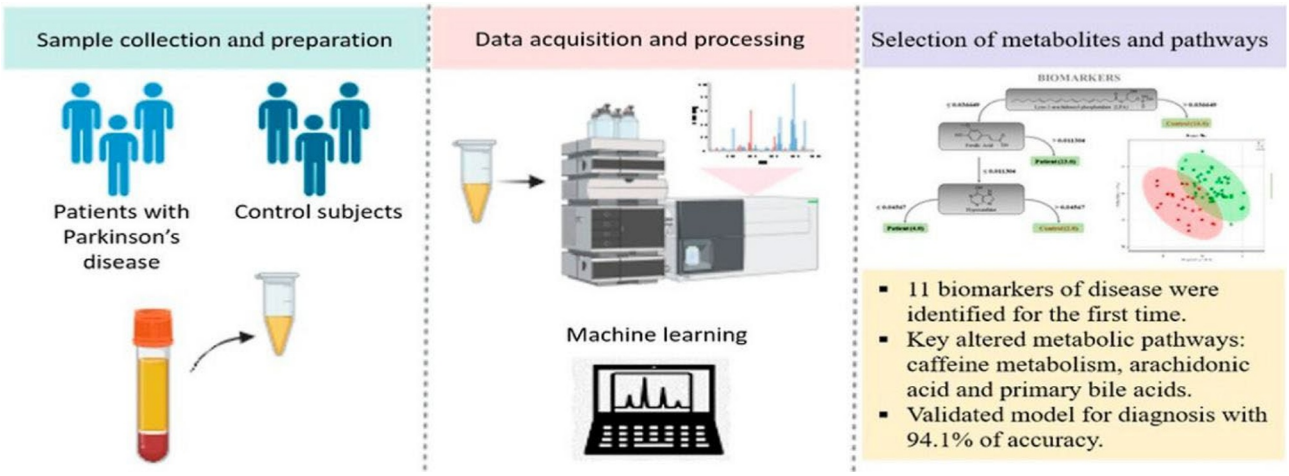


**Figure 3.** Metabolomics reveals pathways of destruction in Parkinson's disease: biomarker-based diagnosis.

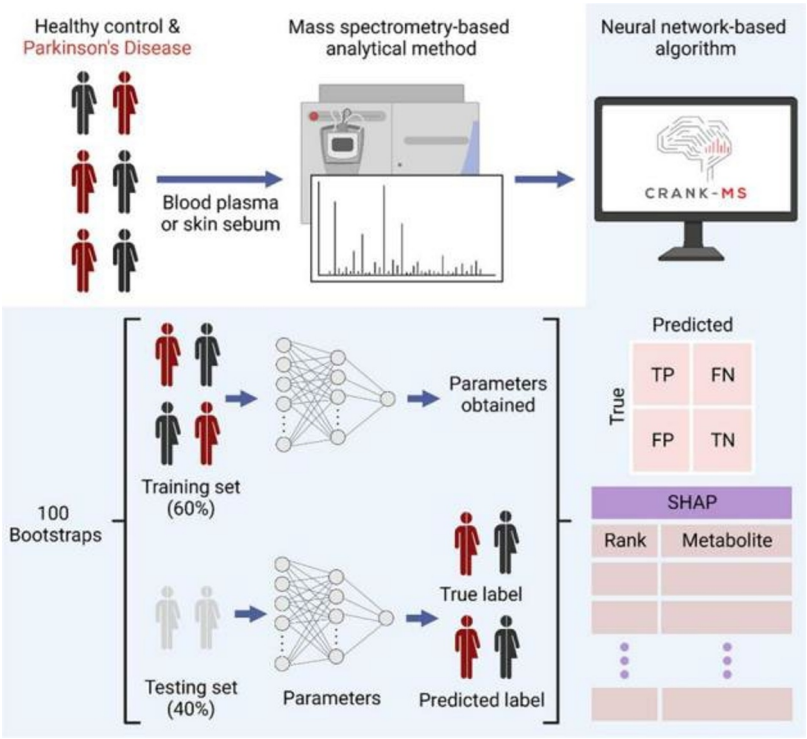


**Figure 4.** Neural network framework for predicting Parkinson's disease using large-scale mass spectrometry-based metabolomics data.

For example, Santos et al. identified several biomarkers associated with PD through metabolomics studies on serum samples from PD patients and healthy controls [4]. These biomarkers include 1-Lyso-2-arachidonoyl phospholipids, N-docosahexaenoyl GABA, paraxanthine, and caffeine. Using LC-MS (Liquid Chromatography-Mass Spectrometry), the researchers accurately measured the differential expression of these metabolites between PD patients and healthy individuals. They further analyzed the mechanisms of these metabolites in disease progression through bioinformatics tools.

In addition, a study by Lan et al. highlighted the crucial role of lipid metabolism in PD [5]. By analyzing lipid metabolites from PD patients and healthy controls, they identified 30 differential metabolites, with

significant enrichment observed in the sphingolipid metabolic pathway. These abnormal alterations in lipid metabolites may be closely linked to the neuroinflammatory and neurodegenerative changes seen in PD, offering valuable insights for further research into the disease's pathogenesis.

### 2.2 Analysis of metabolic pathways associated with Parkinson's disease

The study of metabolic pathways is a core component of metabolomics. By analyzing disease-related pathways, researchers can uncover the dynamics of metabolites in Parkinson's disease and their impact on biological systems [6]. In PD research, several metabolic pathways have been closely linked to the disease's pathogenesis, with the xanthine metabolic pathway and the amino acid metabolic pathway being the most notable.

The xanthine metabolic pathway is believed to play a crucial role in PD's pathogenesis. Lope et al. found that xanthine and its metabolites were significantly elevated in PD patients by analyzing plasma metabolites from both PD patients and healthy controls [7]. Further network analysis suggested that hypoxanthine phosphoribosyltransferase 1 (HPRT1) may be a key regulator of this pathway. This discovery offers a new therapeutic direction, focusing on targeting xanthine metabolism in PD treatment.

Additionally, amino acid metabolic pathways are also critical in PD research. Zhang et al., through the analysis of amino acid metabolites in brain tissues of PD patients, observed significant alterations in several amino acids, particularly glutamic acid, arginine, and alanine [8]. These disruptions in amino acid metabolism may be related to neuronal dysfunction in PD, offering fresh insights into the pathological mechanisms underlying the disease.

### 2.3 Non-targeted versus targeted metabolomics techniques

Two primary technical approaches are commonly employed in metabolomics research: untargeted metabolomics and targeted metabolomics [9]. Untargeted metabolomics broadly tests all metabolites in a sample to identify potential disease markers, while targeted metabolomics focuses on a more in-depth investigation of known metabolic pathways and metabolites.

The advantage of untargeted metabolomics lies in its ability to capture the full spectrum of metabolite dynamics in a sample, making it particularly suitable for studying complex diseases where the underlying metabolic mechanisms remain unclear. In recent years, with advancements in mass spectrometry, untargeted metabolomics has achieved significant progress in identifying PD biomarkers. For instance, Chen et al. applied untargeted metabolomics analysis to identify multiple metabolites closely associated with PD, elucidating their metabolic pathways through bioinformatics, which provided essential data for further research.

Conversely, targeted metabolomics is often used to validate specific mechanisms within known metabolic pathways and markers. This approach enables precise detection of dynamic changes in specific metabolites, making it a valuable tool for in-depth disease studies and drug target validation. In Parkinson's disease treatment studies, for example, researchers have utilized targeted metabolomics to assess the effects of specific drugs on metabolite levels in PD patients, gaining a deeper understanding of drug mechanisms of action.

## 3 Metabolomics in drug evaluation

### 3.1 Evaluation of the effectiveness of drug treatment

Metabolomics can be utilized not only for disease diagnosis but also for evaluating the effectiveness of drug treatments. While current PD treatments primarily focus on symptomatic relief, metabolomics offers a new approach to assess drug efficacy at the molecular level by analyzing changes in metabolites within the body.

In a study on curcumin for Parkinson's disease, researchers discovered that curcumin significantly improved the metabolic status of PD mice through metabolomic analysis [10]. By quantifying metabolite changes before and after treatment, they identified several metabolites closely linked to PD symptoms, which returned to near-normal levels after curcumin administration, suggesting its potential therapeutic effect.

Similarly, Zhang et al. demonstrated that the Chinese herb Baichanting has protective effects against PD [8]. Through metabolomics, they identified 25 endogenous metabolites whose changes indicated that Baichanting may slow PD progression by regulating metabolic pathways such as methionine and histidine. This study provides scientific evidence for using traditional Chinese medicine in PD treatment and highlights the significant potential of metabolomics in drug development.

### 3.2 Evaluation of drug safety

Safety evaluation of drugs is a critical step in drug development, and traditional animal experiments and clinical trials often face challenges such as long durations and high costs. In recent years, the combination of metabolomics and organ-on-chip technology has introduced a new strategy for drug safety evaluation. Organ chips are miniature systems that can simulate the functions of human organs, allowing researchers to assess drug effects on specific organs or systems by replicating human physiological and pathological states in vitro, all in a shorter time frame.

For instance, Wang et al. evaluated the safety of the Parkinson's disease drug tolcapone using organ-chip technology alongside metabolomics [11]. By analyzing the drug's metabolites, they identified tolcapone's metabolic pathways in humans and examined its potential impact on other endogenous metabolites (Figure 5). This approach effectively reduces the need for

animal experiments and offers a more efficient and safer tool for the development of new drugs.

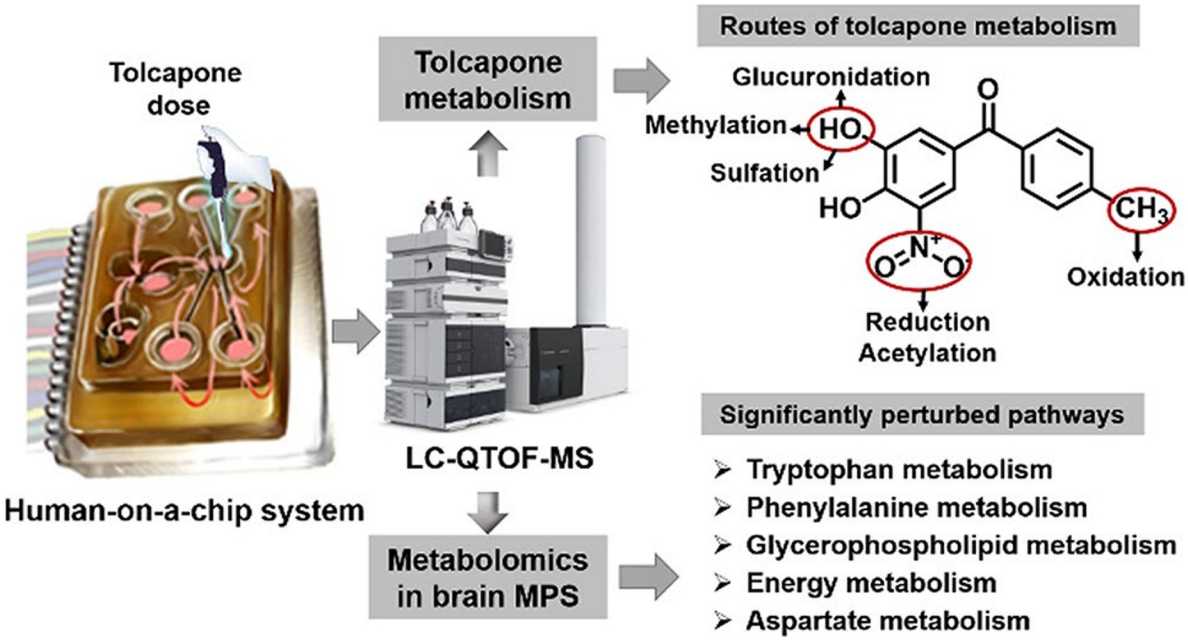


**Figure 5.** Combination of metabolomics and organ microarrays for safety evaluation of the PD drug tolcapone.

## 4 Future prospects

As metabolomics technology advances, its potential in PD research is becoming increasingly evident. Future studies are expected to integrate multi-omics data, including genomics, proteomics, and transcriptomics, to build a more comprehensive framework for understanding PD (Figure 6). Additionally, combining metabolomics with advanced algorithms such as machine learning may enhance the accuracy of disease diagnosis and drug evaluation, leading to more precise therapeutic strategies.

However, challenges remain in metabolomics research. For instance, the detection and identification of metabolites still heavily rely on high-precision instruments, and the vast complexity and diversity of metabolites make it challenging to fully analyze disease-related metabolic pathways. Future research should focus on developing more sensitive and efficient metabolite detection technologies, alongside the integration of bioinformatics tools, to better understand the role of metabolites in PD. This combined approach will be crucial in uncovering new mechanisms and therapeutic targets in PD.

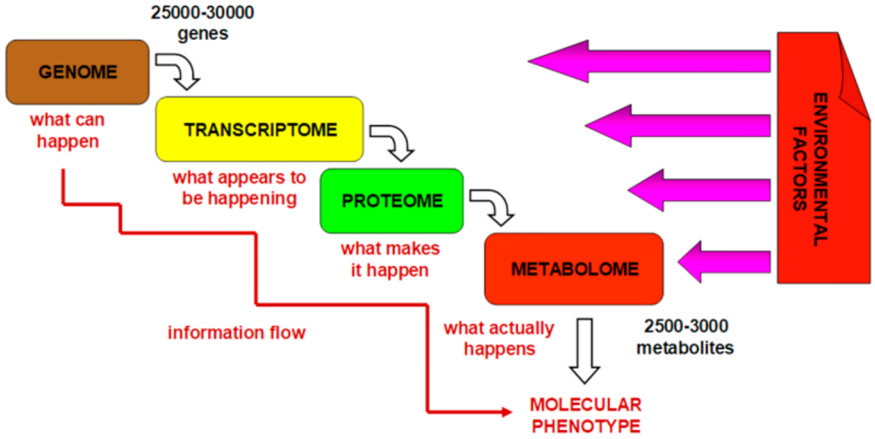


**Figure 6.** Biological systems exhibit complex interactions between the genome, transcriptome, proteome and metabolome.

## 5 Conclusion

The rapid advancement of metabolomics technology has revolutionized Parkinson's disease (PD) research, offering unprecedented opportunities to explore the disease's molecular underpinnings. By identifying specific biomarkers and mapping metabolic pathways associated with PD, metabolomics provides a critical foundation for early diagnosis, enabling intervention at preclinical stages. Additionally, it deepens our understanding of disease pathogenesis, revealing disruptions in energy metabolism, oxidative stress, and neurotransmitter regulation that contribute to

neurodegeneration. Metabolomics also plays a pivotal role in evaluating drug efficacy, facilitating the development of targeted therapies and personalized treatment strategies. As the field evolves, the integration of metabolomics with other advanced technologies, such as artificial intelligence (AI) and multi-omics approaches (e.g., genomics, proteomics), is expected to drive transformative breakthroughs. AI-powered data analysis can uncover complex metabolic signatures, while multi-omics integration offers a holistic view of PD's biological mechanisms. These advancements hold immense promise for developing more effective therapeutic interventions, improving patient outcomes, and potentially slowing or halting disease progression. Ultimately, the continued evolution of metabolomics and its synergy with innovative technologies will significantly enhance PD research, bringing hope to patients and advancing the quest for a cure.

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