

EDITORIAL

New frontiers in Parkinson's disease

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Parkinson's disease (PD) is one of the most common neurodegenerative disorders, representing a growing global health challenge. Traditionally defined by its cardinal manifestations which are purely motor, PD is now increasingly recognized as a complex disorder extending beyond motor dysfunction. Significant nonmotor manifestations precede the emergence of classical motor symptoms and include cognitive, neuropsychiatric, autonomic, sleep, and other non-motor features.

Over the past several decades, the field has moved progressively to shape the variable presentations of PD encountered in clinical practice. Noticeable variability exists in age at onset, predominant symptoms, rate of progression, development of cognitive impairment, treatment response, and long-term disability. This might be inherently related to underlying genetic susceptibility, molecular mechanisms and environmental exposures, which in turn contributed to the definition of the variable clinical subtypes of PD and, ultimately, in developing more individualized approaches to care.

One of the most important frontiers in PD is the effort to identify the disease before the onset of established motor manifestations through identifying prodromal features. Rapid eye movement sleep behavior disorder, hyposmia, autonomic dysfunction, and subtle subclinical motor abnormalities may provide important clues to emerging neurodegeneration. However, no single feature is sufficiently specific to predict progression to PD. The integration of clinical characteristics with genetic, imaging, biochemical, and other biomarkers may therefore allow more accurate identification of individuals at increased risk and provide opportunities for intervention at earlier stages of the disease.

Biomarker development is currently a major focus of PD research. Advances in the detection of pathological α -synuclein and other disease-associated biological signals have created the possibility of complementing the traditional cardinal symptoms-based diagnosis of PD. CSF α -synuclein seed amplification assays identified PD, with pooled sensitivity and specificity of approximately 88% and 95%, respectively.¹ Skin-based detection of pathological α -synuclein,² and serum neuronal exosome also prove promising biotechnologies in PD detection.³ As these technologies mature, they may contribute to a transition from symptom-based classification toward a more biologically based confirmatory diagnosis for that can serve as the basis of research in disease-modifying therapy.

Genetics represents another advancing area. Although most cases of PD are considered sporadic, genes such as *LRK2*, *GBA1*, *SNCA*, and others have provided important insights into the disease mechanisms and permitted identification of variable clinical phenotypes that are not classically recognized.

Parallel advances in neuroimaging not only permit characterization of the structural and functional changes associated with PD but also importantly exclude alternative diagnoses. Imaging techniques may help define patterns of neurodegeneration, clarify disease progression, and distinguish PD from atypical parkinsonism. Imaging

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biomarkers such as DAT-SPECT, cardiac MIBG scintigraphy, neuromelanin-sensitive MRI, quantitative susceptibility mapping, and free-water analysis by diffusion tensor imaging provide complementary measures of dopaminergic loss and nigral microstructural change.⁴ The combination of imaging with molecular and clinical biomarkers may improve diagnostic confidence and facilitate identification of disease subtypes relevant to prognosis and therapeutic selection.

Digital technologies have also emerged as an important new frontier. Wearable sensors and remote monitoring systems can potentially capture aspects of PD that may be difficult to quantify during brief clinical encounters. Motor fluctuations monitoring techniques offer a more comprehensive picture of patients' day-to-day. These technologies support patient access to care, yet validation studies are still required. A recent review of 59 home-monitoring studies found that most studies focused on technical performance or correlations with clinical measures, whereas only nine provided evidence of actual clinical utility, highlighting the need for further validation.⁵

Therapeutic development is undergoing substantial changes. While dopaminergic therapy remains central to the symptomatic treatment of PD, advances in extended-release formulations, infusion therapies, focused ultrasound, deep brain stimulation, and other device-assisted approaches continue to refine management of advanced motor complications. At the same time, considerable effort is being directed toward treatments that target underlying disease mechanisms, including immunotherapies and other approaches aimed at reducing α -synuclein aggregation, therapies targeting lysosomal dysfunction and glucocerebrosidase activity, LRRK2 inhibitors, and strategies addressing mitochondrial dysfunction and neuroinflammation.⁶ The goal is to move beyond symptomatic improvement and toward therapies capable of modifying disease progression.

Rehabilitation and multidisciplinary care remain essential throughout the disease course. Physical therapy, occupational therapy, speech and swallowing therapy, exercise, nutritional support, mental health care, social support, and management of autonomic and cognitive symptoms can substantially affect quality of life and functional independence. Greater integration of these disciplines into longitudinal care models may be particularly important as the population of individuals living with PD continues to increase.

Despite advanced techniques to address these gaps, many challenges remain. The biological mechanisms responsible for disease initiation and progression are

incompletely understood. Established disease-modifying therapies remain an important unmet need. Furthermore, many promising biomarkers and technologies require validation across diverse populations and real-world clinical settings. The translation of scientific discoveries into disease modifying interventions will therefore require continued collaboration within the scientific community.

The Special Issue, "New Frontiers in Parkinson's Disease," aims to provide a platform for emerging research and perspectives that reflect this rapidly evolving landscape. Topics spanning prodromal and early diagnosis, biomarkers, genetics, neuroimaging, α -synuclein biology, novel therapeutics, neuromodulation, rehabilitation, and clinical outcomes are all integral to understanding where the field is heading.

The future of PD care will likely be characterized by earlier recognition, improved measurement of disease activity, and disease-modifying therapeutic strategies. Continued innovation across these frontiers offers the possibility of improving symptomatic care, and also changing the course of PD itself.

Conflict of interest

The author declares no competing interests.

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