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Prioritized Research Recommendations from the National Institute of Neurological Disorders and Stroke *Parkinson's Disease 2014 Conference*

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Parkinson disease (PD) is a serious and rapidly growing public health threat that ranks 24th among all causes of death in the United States.^{1,2} More concerning, PD is the second-fastest increasing cause of US deaths.² Most concerning, continued success in limiting the impact of infectious diseases in the developing world is shifting the burden to noncommunicable diseases, with an expected dramatic rise in global PD in the coming generation of older adults.³

Characteristic motor impairments and brainstem Lewy bodies (LBs) are the classic features of PD. In part because of interventions that effectively mitigate motor symptoms, there is heightened interest in debilitating, nonmotor symptoms of PD, including cognitive impairment, sleep disturbance, neuropsychiatric changes, and autonomic dysfunction that precede motor symptoms in many individuals.^{4,5} PD is a chronic illness that likely begins years prior to full clinical expression; this preclinical period may include a latent stage with no signs or symptoms and a prodromal stage with limited expression of motor and/or nonmotor symptoms.

⁹Listed in Supplementary Appendix.

Our understanding of PD has grown to reveal substantial medical complexity. Other parkinsonian conditions, such as multiple system atrophy, can closely mimic PD, especially early in its course. In addition, LBs accumulate beyond the brainstem, including the autonomic nervous system, gut, salivary glands, and skin, raising the possibility that PD may be viewed more accurately as a systemic illness that prominently manifests as a neurodegenerative disease.⁶ Finally, pathologic changes of PD can exist alongside Alzheimer disease and vascular brain injury, especially in older individuals, and this confounds diagnosis, clinical management, and research.

Medical complexity is further compounded by biological heterogeneity. Knowledge of genetic risk for motor and nonmotor symptoms has advanced greatly and led to the identification of more than 2 dozen independent genetic loci, their products, and the cellular processes that they support; prominent among these are the genes for α -synuclein, DJ-1, LRRK2, PINK1, parkin, and glucocerebrosidase, and the processes of synaptic transmission, mitochondrial function, autophagy, and neuroinflammation.⁷ PD likely derives from multiple molecular drivers that vary among individuals, act over years prior to clinical expression, underlie an individual's ensemble of motor and nonmotor symptoms, and likely dictate response to treatment and its complications.

Dopamine replacement therapy and deep brain stimulation (DBS) are seminal advances in PD health care that are the fruits of previous research; however, they have limitations.⁸ These interventions appear neither to slow substantially the progress of underlying disease nor to have major impact on nonmotor symptoms; rather, they act mostly to alleviate motor symptoms, sometimes with disabling side effects. Appreciating the tremendous achievements made in bringing these treatments to clinic, the community of investigators focused on PD now strives to develop precision medicine⁹ to bring greater clarity to the medical and biological complexity of PD. Key components of this vision of precision medicine include: illuminating fully the overall risk architecture for PD; discovering the molecular mechanisms of disease initiation and progression; developing tools for accurate and early evaluation of disease processes; and implementing safe, effective, and individually tailored interventions with minimal complications.

Recognizing that solutions require further research, the National Institute of Neurological Disorders and Stroke (NINDS), in accordance with the Morris K. Udall Parkinson's Disease Research Act (P.L. 105–78), convened Parkinson's Disease 2014: Advancing Research, Improving Lives to build consensus on priorities in PD research with participation from >600 patients, caregivers, representatives from nongovernmental and nonprofit groups focused on PD, other stakeholders, and researchers in academia, government, and industry from across North America and Europe.

Our efforts began with a request for information that solicited broad community input on scientific opportunities and outstanding needs for research and treatment of PD (NOT-NS-13–035, <http://www.ninds.nih.gov/funding/RFI-PD.htm>). Panels were appointed with experts in basic, translational, and clinical research in PD and related illnesses (Supplementary Appendix). Preconference efforts culminated in prioritized research recommendations that were shared broadly with participants.

Our next step was to hone and organize our research recommendations with broad input and feedback from the larger community of patients, caregivers, advocacy groups, health care providers, and scientists at the Parkinson's Disease 2014: Advancing Research, Improving Lives conference held at the NIH main campus on January 6 and 7, 2014. The final prioritized recommendations for PD research were reviewed and unanimously approved by the NINDS Advisory Council. Our top recommendations are listed in order of priority in the Table. Detailed descriptions of these and the remaining 22 recommendations can be reviewed at <http://www.ninds.nih.gov/research/parkinsonsweb/PD2014/index.htm>.

Several recommendations spanned basic, translational, and clinical research and thereby represent potential opportunities for greatest impact on PD research. These are:

FULL UNDERSTANDING OF THE BIOLOGICAL BASES OF INDIVIDUAL VARIATION AMONG PATIENTS WITH PD

This effort should encompass racial and ethnic background, penetrance of PD genetic risk, motor versus nonmotor symptoms, impact on quality of life, and response to therapies. Among these, genetic risk for PD motor and nonmotor symptoms and their progression is key not only to clinical and translational research, but also to basic research, because the identified genes provide critical clues to the molecules involved.

BRIDGING FROM MOLECULES TO MECHANISMS

This approach can be aided in several ways, including elucidation of normal, as well as abnormal, function of the products of PD genes, development of induced pluripotent stem cells from carriers of genetic variants, and expanded analyses of the cellular pathways involved. There was broad acknowledgment of a central role for the accumulation of abnormal α -synuclein, as well as the need to investigate mechanisms for its apparent spread across brain regions and its interaction(s) with the products of other disease-associated genes.

DEVELOPING TECHNOLOGIES TO MEASURE PD PROCESSES

This key area will provide guidance to basic research and promote precision medicine for PD. Biofluid biomarkers as well as structural and functional neuroimaging will make important contributions. Two specific opportunities noted are biopsy of peripheral tissue that accumulates LBs and monitoring brain circuits as part of DBS. Such monitoring offers great potential for reverse translation from clinical to basic research. A third set of technologies highlighted by our panel is "body-worn" or "smart home" technologies that provide more detailed characterization of an individual's motor, cognitive, and behavioral impairments for use in populations and settings that historically have had limited involvement in research.

The research recommendations presented here will culminate in new approaches that have the potential to prevent, slow, and even stop PD. Success in this ultimate goal can be accelerated by focusing on learning trials, that is, phase 1 and 2 clinical trials, in molecularly stratified subsets of participants that have as their primary endpoint some measure(s) of PD

pathological processes that demonstrate activity at the therapeutic target. Success will require a paradigm shift in our approach to therapeutic development by insisting on the pursuit of targets and pathways with strong scientific and mechanistic rationale, and a clear understanding of the mechanism of action of the intended therapeutic agent. This approach will require biomarkers, neuroimaging, and monitoring technologies that reveal target engagement and target activity so as to provide confidence that the intended therapeutic mechanism can be tested in clinical trials.

Given the nature of discovery, it is with some hesitation that we make recommendations for future research. Nevertheless, the recommendations summarized here form a foundation for precision medicine to bring individual clarity to the medical and biological complexity of PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE**Highest Priority Recommendations in Each Research Topic Area**

Topic Area	Recommendation
Clinical research	1. Define the features and natural history of prodromal PD including progression, events that underlie phenotypic conversion to clinically manifest PD, and biomarkers or other determinants of prodromal subtypes with the goal of providing sufficient rationale to initiate proof-of-concept prevention trials that initially target high-risk populations.
	2. Develop effective treatments and companion biomarkers for dopa-resistant features of PD. These features include both motor symptoms, particularly gait and balance problems, such as freezing of gait, and nonmotor symptoms, especially cognitive impairment, psychosis, and dysautonomia.
	3. Characterize the long-term progression of PD and understand the mechanisms that underlie the heterogeneity in clinical presentation and rates of progression. Factors related to disease heterogeneity may include clusters of clinical features as well as biological factors such as genotype and biomarkers.
Translational research	1. Develop patient stratification tools that define disease signatures of more homogeneous cohorts with emphasis on slow- versus fast-progressing PD, prodromal PD, and nonmotor symptoms.
	2. Develop novel and specific PET imaging agents and assays to measure α -synuclein burden, validated in both animal models and human tissue.
	3. Develop resources with greater power to predict efficacy and biomarker outcomes in clinical trials. These resources would include well-characterized replication sets of iPSC cell lines from sporadic, dominant, and recessive PD cases.
Basic research	1. Develop transmission models of pathologic α -synuclein and tau, and determine the mechanisms of propagation, release, and uptake of misfolded α -synuclein and tau, including the role of "strains."
	2. Elucidate the normal and abnormal function of α -synuclein and its relationship to other PD genes (eg, <i>ATP13A2</i> , <i>GBA</i> , <i>LRRK2</i> , <i>PINK1</i> , and <i>PARK2</i>).
	3. Understand how different cell populations change in their coding properties, firing patterns, and neural circuit dynamics over time; how these changes relate to behavior and motor control; and how therapeutic interventions may affect such changes.

PS = induced pluripotent stem; PD = Parkinson disease; PET = positron emission tomography.