Parkinson's disease: Emerging opportunities through global collaboration

Precision medicine holds enormous promise in enhancing treatment efficacy and revolutionizing therapeutic development, leading to more equitable care. However, to realize this promise in all affected individuals, we need to understand disease in populations other than those traditionally studied. Pursuing this approach pays dividends. The recent discovery of a *GBA1* risk factor for Parkinson's disease (PD) in West Africa, in a collaboration between teams based around the World, is a clear example.[1] First, it is a common risk factor, present in more than 40% of PD patients from Nigeria. Second, further work revealed that this genetic risk is mediated by a novel non-coding mechanism, resulting in lower glucocerebrosidase levels and activity.[2] These findings collectively add significant insight into our understanding of the general role of *GBA1* in PD risk. Still, more importantly, they identify a large, underserved population as potentially appropriate for precision therapeutics.

This work provided *prima facie* evidence of the remarkable impact of genetic research in underserved populations, explicitly enabled through initiatives like the Global Parkinson's Genetics Program (GP2; gp2.org), an effort to accelerate our understanding of the genetic basis of PD and related disorders, through analysing genetic data from 250,000 individuals from around the World. It also immediately highlighted three opportunities in neurodegenerative disease, which, if not capitalized on, will delay the development and testing of therapeutics and limit globally equitable care.

The first of these is phenotyping. Characterization of PD as a clinical and neuropathological entity has predominantly, although not exclusively, been done in patients of Northern European ancestry, giving a potentially skewed impression of PD. A small but growing body of literature suggests that the marked clinical heterogeneity of PD is partly related to genetic ancestry.[3–6] Individuals with PD of different racial and ethnic backgrounds and/or across regions of the world demonstrate variability in a range of motor and nonmotor manifestations, disease progression, and complications related to therapy.[3,7] There are also cultural and sociocultural influences on the experience of disease, and variation in the range and impact of symptoms on patients.[3,4] Incorporating this diversity into the development of patient-reported outcomes, culturally and linguistically appropriate cognitive testing, and other outcomes is essential for capturing the full spectrum of disease, especially as it relates to measures used in clinical trials. Further, as *in vivo* biomarkers of proteinopathy, dopaminergic dysfunction, and other measures of neurodegeneration emerge, testing them in diverse populations will be crucial to identify population-specific reference ranges and cut-offs. A critical component of this effort will be studying the disease longitudinally and across its spectrum, starting in the prodromal or at-risk phase. The emphasis on enrolling participants in trials at the earliest stages of disease, along with the opportunities afforded by early biomarkers, dictates a need and offers a chance to understand disease progression from pre-symptomatic to late-stage.

A second opportunity has arisen, with the rapid progress being made in biomarkers for neurodegeneration, for improving biological understanding of these diseases. We are already on a path to expanding our understanding of the genetic basis of PD in populations worldwide. However, we need to translate genetics into biological understanding rapidly and in a way that is relevant to all populations. Initiatives like GP2 allow the obtaining of suitable ancestry-relevant

biomaterials, such as induced pluripotent stem cells, brain tissue, blood, skin biopsy, CSF, etc, and for the comparison of biomarkers across populations and the establishment of ancestry aware biomarker cutoffs. For the West-African *GBA1* discovery noted above, the variant was common, and thus, the limited African-ancestry transcriptional and proteomic data available were sufficient. Furthermore, the local investigators and the funder (Aligning Science Across Parkinson's, ASAP) were motivated to facilitate the quick and efficient collection and distribution of biosamples. As more ancestry-specific genetic discoveries are made, translating genetics into disease mechanisms will become increasingly challenging, partly due to rare variants and small-effect variants that require large sample series, access to relevant biomaterials, and local infrastructure limitations, among other factors, which will delay progress.

The last immediate opportunity is to facilitate access to clinical trials. We outlined above the need to understand clinical presentation, rate, and progression from the earliest stages, as well as the underlying mechanistic architecture of disease in diverse populations. This understanding will provide a great opportunity in therapeutic development. It offers novel targets, individualized patient trajectories, and populations enriched for definable mechanistic types of disease. However, all this progress in understanding will only bear truly impactful results if we can mobilise industry and investigators to undertake clinical trials in the global PD population. This is not without challenges; many low-income countries lack the robust infrastructure and well-defined regulatory and approval processes required for trials. The most challenging issues relate to the prediction of a low local market opportunity in these populations. This point is mirrored by investigators within underrepresented groups, specifically, the exploitation of populations who may have limited access to treatments after trial conclusion.

Through global collaboration, GP2 aims to accelerate the discovery, testing, and deployment of new therapies by building research capacity, facilitating data democratization and maintaining regular contact with researchers (see panel). There is both a social imperative and a scientific need to take on such work, that will ultimately be for the benefit of all patients with disease. These steps require significant financial resources and groups of established researchers committed to supporting progress beyond that in their laboratory; however, the outcomes of this work will be critically important and will accelerate our path toward a treatment for every patient.

Acknowledgments
This work was supported by the Global Parkinson's Genetics Program (GP2). GP2 is funded by the Aligning Science Across Parkinson's (ASAP) initiative and implemented by The Michael J. Fox Foundation for Parkinson's Research (https://gp2.org). For a complete list of GP2 members, see https://gp2.org.

Competing Interests
HRM has received grant funding and support for attending meetings and/or travel from the Michael J Fox Foundation for Parkinson's Research for this work. HRM received grant funding from the PSP Association, CBD Solutions, Drake Foundation, Parkinson's UK, Medical Research Council UK, and Cure Parkinson's Trust unrelated to this work. HRM has received consulting fees from Roche, Amylyx, and Aprinoia. HRM has received honoraria from Kyowa-

Kirin, BMJ, and the Movement Disorders Society. H. R. M is a co-applicant on a patent application related to C9ORF72 - Method for diagnosing a neurodegenerative disease. HRM serves on the Cure PSP Association Advisory Board, the Association of British Neurologists Movement Disorders Special Interest Group, and the Association of British Neurologists Neurogenetics Advisory Group.

AJN has received grant funding from Parkinson's UK, Barts Charity, Cure Parkinson's, National Institute for Health and Care Research, Innovate UK, Solvemed, the Medical College of Saint Bartholomew's Hospital Trust, Alchemab, Aligning Science Across Parkinson's Global Parkinson's Genetics Program (ASAP-GP2), Michael J Fox Foundation, Tower Hamlets Council and QMUL Impact Fund. AJN has received consulting fees from AstraZeneca, AbbVie, Profile, Bial, Charco Neurotech, Alchemab, Sosei Heptares, Umedeor and Britannia. AJN serves on a Trial Steering Committee for the COBALT clinical trial.

ABS has received grant support from the Aligning Science Across Parkinson's Initiative and the Michael J Fox Foundation for Parkinson's Research. ABS has received an honorarium from the World Laureates Association. ABS has received travel support from the World Laureates Association and the Michael J Fox Foundation for Parkinson's Research. ABS serves on the Scientific Advisory Boards of the Lewy Body Dementia Association and Cajal Neuroscience. ABS spouse owns stock in GeneDx.

CB has received grant support from the Aligning Science Across Parkinson's Initiative.

IFM has received grant support from the National Institutes of Health (1R01NS112499, U01AG076482, R01NS132437), The Michael J. Fox Foundation and the Aligning Science Across Parkinson's Global Parkinson Genetic Program (ASAP-GP2), American Parkinson's Disease Association (APDA) and Department of Veterans Affairs (I01BX005978-01A1). IFM has also received honorarium from the Parkinson's Foundation PD GENEration Steering Committee and Aligning Science Across Parkinson's Global Parkinson Genetic Program (ASAP-GP2).

NUO has received grant support from the Aligning Science Across Parkinson's Initiative, the Michael J Fox Foundation for Parkinson's Research and the United Kingdom National Institute for Health and Care Research (NIHR). NUO has received honoraria from the International Parkinson and Movement Disorder Society (IPMDS). NUO serves on the International Executive Committee (IEC) of the IPMDS.

LMC receives research support from the Michael J Fox Foundation, National Institutes of Health, and University of Pittsburgh, is a study site investigator for a study sponsored by Biogen, received consulting fees from the Michael J Fox Foundation for Parkinson's Research, and receives royalties from Wolters Kluwer.

MTP has no competing interests to declare.

CK has received grant support from the Aligning Science Across Parkinson's Initiative, the Michael J Fox Foundation for Parkinson's Research, and the Deutsche Forschungsgemeinschaft. She receives royalty/license payments from Oxford University Press and Springer Nature, consulting fees from Centogene, Lundbeck Foundation, and Biogen, and honoraria from Bial. CK has received support from the Movement Disorders Society and the Aligning Science Across Parkinson's Initiative for attending meetings.

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1 Rizig M, Bandres-Ciga S, Makarious MB, *et al.* Identification of genetic risk loci and causal insights associated with Parkinson's disease in African and African admixed populations: a genome-wide association study. *Lancet Neurol* 2023; **22**: 1015–25.

2 Álvarez Jerez P, Wild Crea P, Ramos DM, *et al.* African ancestry neurodegeneration risk variant disrupts an intronic branchpoint in GBA1. *Nat Struct Mol Biol* 2024; **31**: 1955–63.

3 Ben-Joseph A, Marshall CR, Lees AJ, Noyce AJ. Ethnic Variation in the Manifestation of Parkinson's Disease: A Narrative Review. *J Parkinsons Dis* 2020; **10**: 31–45.

4 Karacan AV, Kibrit SN, Yekedüz MK, *et al.* Cross-Cultural Differences in Stigma Associated with Parkinson's Disease: A Systematic Review. *J Parkinsons Dis* 2023; **13**: 699–715.

5 Zirra A, Dey KC, Camboe E, *et al.* The East London Parkinson's disease project - a case-control study of Parkinson's Disease in a diverse population. *NPJ Parkinsons Dis* 2025; **11**: 172.

6 Lim S-Y, Tan AH, Ahmad-Annuar A, *et al.* Parkinson's disease in the Western Pacific Region. *Lancet Neurol* 2019; **18**: 865–79.

7 Kaasinen V, Luo S, Martinez-Martin P, Goetz CG, Stebbins GT. Cross-Cultural Differences in Patient Perceptions of Dyskinesia in Parkinson's Disease. *Mov Disord* 2023; **38**: 688–92.