Parkinson's disease is ready for precision medicine

ABSTRACT

In 2015, President Obama announced the Precision Medicine Initiative, an ambitious effort to recruit and study one million individuals in the USA [1]. With a goal of advancing personalized medicine, the President shines an important light on a concept that many in the research and medical communities have long appreciated. We will only get to true cures if we can move away from historical clinical disease definitions, based purely on symptoms to one more nuanced and linked to underlying biology, genetics and pathology.

One needs only to look into oncology for powerful examples of the impact of precision medicine. Many tumors are no longer described by affected organ but by specific genetic changes that may have triggered growth. Although much work still needs to be done – we certainly have not 'cured' cancer – translation of molecular biology into clinical practice has dramatically accelerated the development of treatments to the point that some cancers are now widely considered chronic disease [2].

We believe we are poised to make similar advances in the treatment of complex brain disorders such as Parkinson's disease (PD). Our field has made significant progress in identifying neuropathological and genetic risk and causal factors that may underlie PD. Technological advances in molecular profiling, neuroimaging and remote sensors for clinical assessments position us to better dissect disease subtypes and target therapies to those most likely to benefit. Still, truly transforming PD treatment into a precision approach will require tackling key research and regulatory challenges and the coordinated effort of the entire PD community.

PD is diagnosed by onset of motor symptoms: slowness of movement, muscle rigidity, resting tremor and, in some cases, posture and gait problems. Nonmotor symptoms, including sleep disorders, cognitive dysfunction and digestive problems, are also common. Current treatments focus mostly on restoring movement by replacing lost dopamine, but these medicines lose effectiveness over time and only target a small aspect of the underlying pathology. No treatments exist that slow, stop or reverse the disease.

People with PD vary greatly in severity of their symptoms, rates of progression and responses to therapy. This heterogeneity is a critical barrier to testing potential disease-modifying therapies. The field, and patients, must hope for a silver bullet – one treatment that slows progression of a sufficiently large percentage of enrolled patients to detect a significant change. This challenge sets an incredibly high,

Not to say that progress in smartly segmenting the PD patient population is not happening. Neurologists have long described patients who present predominately with tremor while others exhibit greater issues with posture and gait [3]. However, in reality patients seem to fluctuate between these crude categories over time, making it difficult to link such clinical distinctions to underlying biological differences [4]. Specific variants in genes such as LRRK2 and GBA may define genetic forms of PD, and much research is focused on understanding these subsets and developing targeted therapies [5,6]. Measures of biological factors, such as reduced levels of the protein α-synuclein in spinal fluid or altered levels of urate in blood, may distinguish between some forms or progression rates of PD [7,8]. But, again, the exact link between these biological measures, pathology and clinical presentation is lacking, with only limited progress to date [9].

To develop a precision medicine approach to PD, we need deeper understanding of what goes wrong in people with PD – from molecular dysfunction to clinical symptoms – both before diagnosis and throughout one's journey with the disease. These insights will require significant financial and human capital investment to translate the diverse differences seen in PD into targeted treatments. To get there, we need a comprehensive strategy:

• We must make access to data and biosamples the norm and build infrastructure for standardization and cross-cohort analysis. Studies such as the Parkinson's Progression Markers Initiative and the Parkinson's Disease Biomarker's Program are generating rich clinical, imaging and biological data to decipher PD diversity [10,11] and need to be continued and supported. Data and biosamples from these studies are made widely available to empower state-of-the-art analytics and bioinformatics. That access has led to initial findings of risk models and measurable early disease changes in dopamine loss. Yet many other longitudinal Parkinson's cohorts, including from previous clinical trials, languish under lockdown. There is little requirement or infrastructure to standardize platforms to access, connect and combine these data. This constraint limits the pool for discovery and the power for more definitive conclusions. Greater pressure from funders, regulators and publishers as well as motivation from researchers to contribute data from their cohorts, could solve this challenge and allow for greater use and value from these important studies;

• We must partner with patients and their families. Researchers need substantial involvement of patients and their family members to ensure a diverse and representative picture of PD, and the field must design outreach and engagement efforts toward such partnership. Innovative and culturally relevant recruitment strategies can engage individuals who carry relatively rare genetic risk factors [12] or who are from geographically or ethnically under-represented populations. Leveraging technology such as virtual clinical visits and wearable technology will also support engagement of individuals who

do not have easy access to more traditional clinical centers. Robust retention efforts keep people incentivized to remain in long-term observational studies where tracking of disease progression is critical. We also need more significant education on and funding for brain donation programs as definitive PD diagnosis and pathology mapping still requires postmortem sampling. Finally, study sponsors should provide participants with the study data and results. If patients are truly our partners, we should treat them as such;

• We must generate and link deep molecular profiling and clinical data to build a clearer picture of Parkinson's. Genetic and biological studies point to a number of cellular pathways suggested to contribute to PD: protein mishandling, neuroinflammation, mitochondrial dysfunction and oxidative stress, for example. Hypothesis-based approaches should aim to develop clear links between alterations in these pathways and disease risk, onset and progression. In parallel, 'omics' profiling (genomics, transcriptomics and proteomics) should supplement these focused areas of inquiry to illuminate currently unknown connections to Parkinson's disease. Where possible, studies should collect molecular, clinical, imaging and biological data within the same individuals, and analyses should include both antemortem and postmortem samples for biological mapping of the disease at various clinical stages. Such multidimensional, well-annotated datasets require innovative data management and bioinformatic and analytical platforms and, as previously stated, should be accessible to the wider research community to allow rapid replication and confirmation by others;

• We must drive biomarker validation toward a precision-medicine approach. With increased disease understanding, we can identify additional biological targets and pathways associated with PD. And we can use this knowledge to generate well-validated, standardized and clinically feasible biomarkers to segregate patients into biologically relevant disease subtypes. Already, the imaging tool DATscan provides a significant resource to identify patients with dopaminergic dysfunction, which is particularly powerful for inclusion into trials targeting early disease. However, we need a much wider array of imaging and biochemical markers to capture the potential biological diversity underlying PD and atypical forms of parkinsonism. The next step would be partnership with industry to translate findings into useful assays and integration into clinical studies;

• We need to rethink our approach to drug development for brain diseases. Many biological pathways underlying PD are also linked to other neurological disorders. But therapies targeting shared biology are tested in each disease one-by-one, usually based on a variety of scientific and business factors. Maybe there is another way? We envision a day, with both drugs and disease-relevant biomarkers in hand, where drug makers develop and test treatments that target biological dysfunction regardless of specific clinical disease definition. No doubt this will require a fundamental shift in how researchers, clinicians, industry, funders and regulatory agencies work together.

Expanding fledgling work on patient-centered outcomes will be critical, and we will need to re-evaluate risk-benefit assessments as we focus treatments on those with a greater chance of success.

None of these recommendations are simple, but we are already making progress. We continue to tease apart Parkinson's genetics, which points us to biological pathways for disease mapping and drug development. And data from current large-scale studies are providing initial glimpses of the progression of clinical symptoms and putative biomarkers. But much more work is needed, and not all of it scientific. Truly achieving Parkinson's precision medicine means dismantling a centuries-old approach to disease diagnosis and care and adopting a more biology-centric view. And with an aging population at ever greater risk for developing diseases such a PD, the time is now to make the investment and commitment needed to find the breakthrough therapies that all of us so desperately desire.

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