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Predicting progression in patients with Parkinson's disease

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A major challenge to patients, clinicians, family members, and scientists is the unpredictable future that accompanies a diagnosis of Parkinson's disease. When met with the question "what does my future hold?" it is difficult to give predictions that are likely to be useful to the patient. Some individuals will face features that rapidly and adversely affect their quality of life; others will experience a prolonged and fairly benign course, initially well managed by drugs and lifestyle changes. Variability between patients in core features of this multisystem disease—eg, motor decline, neuropsychiatric changes, mood disorders, dysautonomic signs, and fatigue—is the rule.

Variability in the velocity of clinical progression of Parkinson's disease is also a major challenge to researchers and an especially expensive and vexing problem for clinical trialists. In the context of clinical trials, unknown variability in progression has to be accommodated by increased power and longer trial duration, both of which are costly. The growing trend towards running disease-modifying clinical trials in early-stage disease exacerbates this problem substantially, because the course of early disease is especially unpredictable.

In *The Lancet Neurology*, Jeanne Latourelle and colleagues describe their attempts to identify predictors of motor symptoms by using an unbiased machine-learning approach.[1] As the basis of their work, the investigators used data from two observational clinical studies in patients with Parkinson's disease and healthy controls, including data from genetics, imaging, biologics, and clinical assessments: the Parkinson Progression Markers Initiative (PPMI),[2,3] and the Longitudinal and Biomarker Study in Parkinson Disease (LABS-PD).[4] Latourelle and colleagues aimed to construct a clinically useful predictive model of Parkinson's disease motor progression based on previously established and potential novel markers. The outcome measure they used is the Movement Disorder Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS) parts II and III,[5] which has been used widely for assessment of the severity of motor symptoms.

Latourelle and colleagues noted higher baseline motor score, increased age, and male sex to be associated directly with the rate of motor progression. CSF protein biomarkers (mainly α-synuclein) showed a pronounced inverse effect on motor progression prediction in the

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PPMI cohort, but a paucity of data in the LABS-PD cohort did not afford the opportunity for replication. No association was recorded for any imaging markers, suggesting scant prognostic utility. Such findings are in contrast with those of previous studies in which imaging was a predictor of long-term motor outcomes and, when based on the same PPMI data, imaging in combination with genetics was used to predict MDS-UPDRS scores.[6,7]

One of the most relevant features for prediction of motor symptom progression was genetic variation (roughly 3%), despite inclusion of a fairly small number of variants (about 18 000). Conventional genotyping arrays contain more than half a million single nucleotide polymorphisms (SNPs), which are generally used to predict tens of millions of variants. This process raises the question of what the genetic contribution to motor symptom progression would be when using a larger and, therefore, more representative genetic background. Additionally, more accurate prediction could be made if rare disease-linked variants were incorporated—eg, mutations in the glucocerebrosidase gene (*GBA*).[8] The authors also identified a novel gene–gene interaction for variants not previously related to Parkinson's disease risk—namely, the intronic *LINGO2* rs929887 and the intergenic 2q14.1 rs17710829 variant. Although this result, which was associated with faster motor progression, is intriguing, it warrants replication, particularly in view of the known challenges of reliably detecting gene–gene effects.

The study by Latourelle and colleagues adds substantial value to the area of Parkinson's disease research, not only because of the findings described but also because it introduces the topic of using multimodal data in disease prediction, an approach that is sure to grow in popularity and one that is complex in its application and interpretation. With any study such as this, important caveats must be taken into account. Both the discovery and replication efforts are of somewhat limited power with respect to sample size and substantial differences exist between the cohorts. Harmonisation of future cohorts and standardisation in collection of progression data, including motor assessments and homogeneous follow-up time distributions, are needed to provide an accurate assessment of a marker's sensitivity and specificity. Clearly, there is a requirement for the expansion of such efforts both in terms of sample size and length of follow-up.

This study marks a movement in the development of methods to predict disease progression and, therefore, assist clinicians, patients with Parkinson's disease, and their family members with treatment and individualised disease management.[9] The potential to reduce variability in clinical trials is vital. We are entering an exciting era, moving from describing to predicting disease features. Although this methodology of research is promising, fine-tuning of these models and extension of current efforts are key. Although these endeavours are expensive, they are vital in our development of disease-modifying therapies and in the ultimate treatment of Parkinson's disease.

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