Title

The Ethical Landscape of Prodromal Parkinson Disease: Considerations for Shared Decision-Making and Health Equity.

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Rapid advances in identification of biomarkers for Parkinson disease (PD) have enabled identification of neuropathology in asymptomatic individuals, leading to proposals for new preclinical and prodromal diagnostic categories intended to facilitate research and accelerate the development of disease modifying therapies[2,3]. In this issue of NEUROLOGY, Rees et al. publish a paper in which they explore the ethical implications of disclosing a diagnosis of prodromal Parkinson's disease[1]. The authors outline important benefits a prodromal PD diagnosis could provide for patients, such as opportunities and motivation to enroll in clinical trials, implement lifestyle changes, and manage personal, social, and legal affairs. However, they also describe potential harms including psychological distress, social stigmatization, and discrimination; as well as societal concerns such as impacts on insurance markets. Given the complexity of balancing these factors for each patient, the authors argue that there is no "one-size-fits-all" approach to disclosure. Here, we draw on guidance from other clinical domains to recommend shared decision making as a model for navigating these issues and call for broader data to advance neurologic health equity.

Biomarkers for PD-related neuropathology are detectable before the onset of clinical signs and symptoms[2,3]. Given the slow, uncertain, and nonlinear progression from prodromal states to functional impairment, many biomarker-positive people will not experience any significant symptoms during life. For those who do progress, this timeline may range from months to decades, particularly for carriers of

monogenic mutations who could be identified at any age. While disclosure offers the potential of benefit from experimental treatments in clinical trials, no disease-modifying treatments have been demonstrated for PD, and the availability of such treatments is a critical factor in whether patients report wanting to learn of a prodromal diagnosis[4,5]. Furthermore, current US law provides unclear legal protections for individuals with preclinical or prodromal diagnoses, highlighting the vulnerability of this new population of “patients-in-waiting” to insurance and employment discrimination[4,6]. Thus, decisions to disclose prodromal PD status will depend on patients’ personal values, preferences, and needs, which must be elicited without prematurely raising the specter of a feared neurodegenerative disease.

In clinical scenarios without a “one-size-fits-all” approach, patient priorities determine the best treatment to offer and even when and how information should be presented. These are referred to as "preference-sensitive conditions," which call for a patient-centered care strategy known as shared decision making[7]. Under this model, patients are experts in their personal values and preferences, and clinicians provide expertise on options and their relative risks and benefits. Contributions from each partner to the discussion improve understanding of how to weigh the various factors and promote shared responsibility for the decision. For example, screening for prostate cancer offers small benefits in life expectancy but also has known risks including false positives and treatment complications such as incontinence or erectile dysfunction for tumors that may not have affected the patient during life. Consequently, current recommendations are to understand each patient’s history and preferences, share information on risks and benefits, and only screen if patients that express a preference for screening[8]. For prodromal PD, factors such as the

patient's prognosis and their propensity and eligibility to participate in clinical trials should be considered to determine whether disclosure offers net benefit. The risk of inadvertent, unwanted disclosure will continue to increase as predictive testing becomes more common for PD and other neurodegenerative conditions such as Alzheimer's disease. One potential approach to obtain relevant information in anticipation of neurodegenerative screening decisions would be to elicit and document patient values and preferences during advance care planning. Notably, as these techniques make their way into broader clinical practice, this burden will likely shift to primary care practitioners, meaning the field should prioritize increasing their capacity to advise and refer these patients appropriately.

Rees et al. also highlight the lack of diversity in data on patient perspectives and clinical efficacy as a critical barrier to equity in prodromal PD[1]. Most clinical trials on PD biomarkers and genetic data sample largely White populations in Western countries, but the limited data available to date suggest there may be important group differences relevant to prodromal PD screening and diagnosis decisions, such as variation in the prevalence of genetic risk factors for PD across populations[9]. Moreover, cultural or locality differences in clinical disclosure practices, social norms, caregiving support systems, and governmental policy could influence the net impact of a prodromal PD diagnosis and thus patient preferences for disclosure. Similarly, most studies on patient perspectives on early diagnosis and risk disclosure lack diversity and focus on monogenic conditions or particular at-risk groups[4,5], so the generalizability of these studies is unclear. Further research on clinical validity and patient perspectives prodromal PD diagnoses in diverse samples is needed to close these gaps and to establish ethical and culturally sensitive clinical practices.

Overall, current frameworks for preclinical categorization of PD are explicitly intended for research only[2,3], but implementing predictive testing in research and clinical settings will rapidly expand the number of patients vulnerable to harms. Failure to protect this burgeoning population of “at risk” patients may discourage clinical trial enrollment and counteract the potential gains in understanding the disease and developing treatments. These issues are accentuated for members of underrepresented groups, who are less likely to benefit directly from trial enrollment and from subsequent findings that may not generalize to their care. Importantly, shared decision making has been shown to improve health outcomes for disadvantaged groups[10], indicating that this patient-centered framework can also promote the equitable distribution of benefits and risks in prodromal PD diagnosis.

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