# Feasibility of Huntington disease trials in the disease prodrome

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In this issue of *Neurology*®, Rosas et al.[1] present a phase II trial of creatine in Huntington disease (HD). This study is remarkable not only for the demonstration of safety and tolerability but also because the study design establishes the feasibility of clinical trials among premanifest HD individuals. Notably, the trial is undertaken in the disease prodrome, when the participants are clinically unaffected by HD, rather than in established disease. Furthermore, not all participants knew their mutation carrier status. The trial design defines methods to preserve confidentiality and overcomes the difficulty of studying HD at its earliest phase by avoiding the requirement to include only the genetically tested. The success of this study demonstrates that sufficient discriminant power can be obtained without the exclusion of genetically untested at-risk individuals.

This trial uses neuroimaging measures validated in established disease. Other markers of change (motor, cognitive, psychiatric, etc.) within the HD prodrome and leading to a definite clinical diagnosis were utilized; these derive predominantly from the multicenter prolonged observational trials (Predict-HD and TRACK-HD[2,3]) that compared clinically unaffected carriers with non–mutation carriers, an ideal control group.

The Holy Grail for diseases such as HD, whereby mutation carriers can be identified before disease manifestations, is to develop a therapeutic intervention to delay disease expression. This study investigates a potentially neuroprotective agent designed to delay disease onset. Twenty years ago, when the HD mutation was identified,[4] there was great interest in genetic testing before disease onset. However, for reasons that include fear of discrimination and lack of treatment, only approximately 20% of eligible at-risk individuals undergo testing. As discussed, the ethical challenges for those recruiting and conducting trials include how to accommodate nontested at-risk individuals while preserving a noncoercive choice regarding genetic testing.[5] The recognition that unequivocal changes occur in the prodrome 15 to 20 years before conventional clinic-based diagnosis[2,3] imposes another dimension of concern for at-risk individuals, while simultaneously opening an opportunity for clinical trials. Prodromal biomarkers permit trials of prospective disease-modifying treatments before irreversible cell loss.[6] Unlike Alzheimer disease, Parkinson disease, or other neurodegenerative disorders, HD has a single etiology[7] and is ideal to pioneer trials in the prodromal phase.

Prodromal trials also avoid the disease-related impediments to recruitment when consent is complicated by cognitive changes, disability, and caregiver burden. Furthermore, trials can be performed without the confounding effects of symptomatic treatments. In HD, it may prove more efficacious to document a decline in function from normality or a delay to onset than to document slowing of an established disease progress. Furthermore, many at-risk individuals, desperate to avoid disease onset, turn to unsubstantiated supplements. Earlier trials could divert this understandable desire to take anything rumored to be beneficial toward finding evidence-based interventions.

Nonetheless, the study of the prodrome is not without complexity. The trial design must be subject to rigorous statistical analysis and power calculations to avoid expensive but inconclusive assessments and investigations. Measures must be sufficiently objective to detect reliably subtle changes in test batteries implemented across multiple sites with multiple examiners over years of testing. Trial measures must be sensitive to the varied features of prodromal disease, which may differ considerably from one individual to the next (e.g., predominantly cognitive-onset vs predominantly motor-onset). In this trial, only neuroimaging was a reliable measure of progression and may be the most appropriate primary outcome measure in future studies. The fact that the mutation carriers could range from far-from-onset to mid- and near-onset must be accommodated in trial design.

While trials in the prodrome that include nontested at-risk persons increase the potential pool of participants from 20% to 100%, other aspects of ethical import must be considered. Traditionally, carriers have been counseled that although they have the mutation, the disease has not yet developed.

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However, now that brain-related changes in the prodrome are irrefutable, trial participation could create concern about these changes and possibly the chance for discrimination.[8,9] Maintenance of privacy will remain a challenge. Not only may some participants request information about their brain volumes, but employers or others may wish to acquire or subpoena this information. Methods to appropriately address the onset of disease manifestations during the trial in a participant who expressly requested not to know his or her HD status poses a dilemma for neurologists conducting trials. Periodic assessment by an independent "treating neurologist" will be a requirement.

Furthermore, it is not known how readily individuals will participate in such studies, although the trial by Rosas et al. successfully recruited, in a timely manner and in adequate numbers, the at-risk group, which continued in the trial. The potential that future trial interventions may have substantial side effects will present another dilemma in a healthy (noncarrier at-risk) group, as well as those mutation carriers far from onset.

Finally, the issue of "when is a disease a disease" must be reconsidered. If we were to regard neurodegenerating cells as we do cancer cells, there would be immediate action at the first sign of disease. Definition of the prodrome is well advanced, but further refinement of the tools for staging the prodrome can be expected. Thus, our perspective evolves to one that permits trial interventions at ever-earlier stages. We may contemplate treatments among minors if there is likely clinical benefit. Although not trivial, these issues should not deter us from embracing the long-sought era of preventive medicine in neurodegenerative diseases. With recognition of additional genetic predispositions for these diseases, this more inclusive clinical trial design should establish the precedent not only for HD but for other neurodegenerative diseases as well.[10]


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## DISCLOSURE

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