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Establishing a clinical trial battery for Huntington disease

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Abstract

The success of clinical trials in Huntington disease (HD) will depend to a large degree on the quality of the outcome measures. Using data from the TRACK-HD study, a recent publication proposes a battery of assessments that could be used as outcomes in future clinical trials in patients with early HD.

A limitation to the care of Huntington disease (HD) is a dearth of proven treatment options. At least 16 distinct compounds have been tested through human clinical trials, [1,2] and a few animal models of stem cell replacement [3] have also been generated. Several refined and new compounds, as well as efforts to reduce the expression of the mutant huntingtin gene, are now being incorporated into the design of clinical trials. The success of all efforts to improve the care of people with HD depends on the development and validation of objective, quantifiable and feasible outcome measures.[•]

A recent publication by Tabrizi and colleagues in *The Lancet Neurology*[5] describes results for various outcome measures in the TRACK-HD study. TRACK-HD is a prospective, four-site, longitudinal study designed to quantify possible outcomes in HD. Tabrizi *et al.* report 24-month data for 116 healthy control individuals, 117 pre-manifest gene carriers, and 116 participants with a clinical diagnosis of HD. Premanifest participants were classified at baseline into two groups, preHD-A and preHD-B, on the basis of predicted proximity to HD diagnosis, with the latter group being closest to diagnosis. Participants with an HD diagnosis were also classified into two groups (HDl and HD2) according to their level of functioning (HD 1>HD2). An additional two groups, progressors and non-progressors, were later formed from the premanifest participants on the basis of presence or absence, respectively, of appreciable progression over time.

With the 91% of participants who were retained from baseline assessments, a range of variables was monitored over the 24-month period. These variables included clinical ratings of motor abnormality, functional capacity and psychiatric symptoms; objective standardized assessments of cognition and quantitative motor measures; and neuroimaging measures derived from 3T MRI brain scans. Of 21 outcome measures reported (using P<0.01 for

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multiple comparisons), 17 showed significant differences for participants with HD (HD 1 plus HD2) when compared with changes in normal controls. For the premanifest gene carrier groups, only three measures -putamen volumes, caudate volumes, and total motor score-showed significant changes when compared with normal controls. Three additional MRI measures showed significant brain volume changes in progressors relative to non-progressors.

Among the six imaging measures that were considered, change rates for putamen and caudate volumes were significantly greater in all HD groups than in healthy controls. Three measures -whole-brain volume, ventricular volume, and white matter volume-were significantly different from control values in both the diagnosed HD and preHD-B groups, whereas changes in grey matter only diverged from control values in the diagnosed HD groups. The diagnosed groups differed significantly from the controls on four of five cognitive outcome scores (symbol digit modality test, Stroop word reading, circle tracing-direct, and circle tracing-indirect). None of the 24-month change scores for the cognitive outcomes showed significant variations between the premanifost gene carrier group and the controls. Of five quantitative motor scores that were compared across groups, chorea position, grip force variability and tapping speed measures all differed markedly between the control and diagnosed HD groups. Clinical motor rating scale scores were significantly different for all HD groups when compared with normal control changes, whereas changes on functional capacity and apathy were only significantly different for the diagnosed groups.

The results of the Tabrizi *et al.* study culminate in a table of TRACK-HD assessments that are proposed to be used as outcome measures for future clinical trials in early HD. The authors also provide sample size and statistical power calculations for different effect sizes in the recommended battery of measures.

TRACK-HD has met the stated goals, and has provided excellent multisite, prospective, longitudinal data for 24-month followup of a cohort of early-stage and premanifest individuals with HD. The four sites and the CHDI leadership should be lauded for this efficient study, and other disease specialties and academic groups could benefit from adopting this type of paradigm. However, the integration of the Tabrizi *et al.* data into the extant literature and its utility for perpetual research endeavours require careful consideration. The analysis focused on statistical effect size, but each candidate measure within a clinical battery should also be evaluated in terms of feasibility (for example, cost), psychometric rigour (for example, reliability across sites), normative standards (stage of disease as well as normal control variation), and participant burden (for example, frustration level).

The Tabrizi *et al.* analysis considered each variable in isolation, so the issue of unique contribution of individual measures was not addressed. A multivariate approach -though not easy to perform-would provide information about the specific utility and power of individual measures above and beyond the numerous measures already available. The proposed battery might then be reduced even further by eliminating redundancy without sacrificing efficiency. For example, motor impairment might validly be indexed by a subset of the six measures considered in the analysis.

A challenge in any study of HD is the classification of disease progression at the start of the study. Accurate classification is essential to identifying which tools are appropriate markers for particular individuals. Tabrizi *et al.* go along way in this regard by using the thoughtful classification strategy previously mentioned. As with all ordered categories of progression based on multiple criteria, it is unclear what portions of the disease progression spectrum are represented by the groups. For example, the traditional definition of motor diagnosis might be too cautious. In addition, a gap, representing an intermediate status, might exist between the premanifest and manifest groups. This scenario is depicted in Figure 1, which shows the four initial Tabrizi *et al.* groups depicted by solid boxes, and the potentially omitted group represented by the dashed box.

The results of the study showed an appreciable increase in effect size when stepping up from preHD-B to HD l. Inclusion of intermediate groups might be helpful in determining whether effect-size change is gradual or sudden. The potential benefit of such an approach is the identification of critical points along the disease progression at which particular tools gain or lose sensitivity. Such information is important to maximize resources for future clinical trials.

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Figure 1.

HO progression groups located on a hypothetical spectrum. The dashed box indicates a possible intermediate status between the premanifest (preHO) and manifest (HO) groups. Abbreviation: HD, Huntington disease.