RESEARCH ARTICLE

Utility of the Huntington's Disease Prognostic Index Score for a Perimanifest Clinical Trial

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ABSTRACT: Background: Subtle neurodegenerative motor and cognitive impairments accumulate over a prodromal period several years before clinical diagnosis of Huntington's disease (HD). The inclusion of prodromal individuals in therapeutic trials would facilitate testing of therapies early in the disease course and the development of treatments intended to prevent or delay disability.
Objectives: We evaluate the normalized prognostic index (PIN) score as a tool to select participants for a perimanifest trial. We explore anticipated PIN-based inclusion rates from the preHD screening population and estimate sample-size requirements based on PIN threshold, trial duration, and outcome measure.
Methods: Individual participant data from ENROLL-HD were used to fit mixed effect linear models to assess longitudinal changes in clinical metrics for participants with early-manifest HD and PIN-stratified preHD subcohorts.
Results: A PIN threshold of 0.0 was met by 40% of the preHD participants in ENROLL-HD; 39.4% and 55.2% progressed to new diagnoses of early-manifest HD within 2 and 3 years, respectively. Various PIN thresholds also enabled the selection of specified ratios of prodromal preHD to early manifest HD participants for a perimanifest trial. Estimated sample sizes for a trial enrolling prodromal preHD (PIN > 0.0) and stage 1 and 2 motor-diagnosed participants varied depending on the composition of the screening pool, the length of follow-up (1, 2, or 3 years), and outcome measure.
Conclusions: The composition of a perimanifest clinical trial population can be defined using preselected PIN thresholds, facilitating the assessment of potential disease-modifying therapies in HD. © 2022 Voyager Therapeutics, Inc. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson Movement Disorder Society.

Key Words: Huntington's disease; prodromal; prognostic index; clinical trial design

Huntington's disease (HD) is an inherited, progressive neurodegenerative disease caused by a CAG expansion in the huntingtin (*HTT*) gene. In patients with HD, motor, cognitive, and neuropsychiatric impairments subtly accumulate over a period of many years before clinical diagnosis.[1-4]

Various terminologies have been proposed to describe the early stages of the natural history of HD, although consensus is lacking.[4-6] We find the following terminology

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useful: *premanifest HD* (preHD) refers to mutant *HTT* carriers who have not yet received a clinical diagnosis of HD (note: the most commonly used definition of *diagnosis*, which we follow in this study, is a clinician's rating of 4 [highest] on the motor diagnostic certainty item of the Unified Huntington's Disease Rating Scale [UHDRS]). *Prodromal HD* refers to preHD individuals who have observable motor, cognitive, and behavioral symptoms that are suggestive of HD but fall short of the UHDRS threshold for diagnosis. *Perimanifest HD* refers to the continuum of individuals with late-prodromal or early-manifest (ie, early-diagnosed) HD.[4-6] (The challenge of defining and identifying "late" prodromal will be the topic of this report.) Although there have been large-scale natural history studies of prodromal symptoms and biomarkers and transitions to clinical diagnosis,[1-3] most therapeutic trials have enrolled participants with diagnosed, early-manifest HD and excluded participants with prodromal HD.[6] A common entry criterion is stage 1- or 2-diagnosed HD, corresponding to the UHDRS total functional capacity (TFC) scores of 11 to 13 and 7 to 10, respectively.[4,6] Trials that have included prodromal individuals have demonstrated their feasibility[7-9]; however, design parameters for optimizing such trials to enable demonstration of a clinical benefit remain uncertain.

Emerging treatments for HD, including gene-targeted therapies designed to reduce the expression of the mutant huntingtin protein, have the potential to halt or slow the progression of HD.[4,6] Ideally, these therapies would be administered as early as possible in the disease process, including in those who do not yet have sufficiently overt signs and symptoms to support a clinical diagnosis. Nevertheless, the demonstration of a measurable clinical benefit is most feasible when there are measurable clinical signs.

A perimanifest patient population has advantages for clinical trials of HD as it would both increase the available candidate pool and provide a broader scope for assessing potential disease-modifying therapies and their effects at an earlier stage of disease. However, a perimanifest population also poses challenges. Although the rate of pathological progression within the brain accelerates during the prodromal period,[1,10] progression, as measured by existing clinical outcome measures, is slower in prodromal than in manifest HD. In practical terms, the inclusion of prodromal individuals can reduce trial efficiency by reducing the statistical power of clinical outcomes and necessitate the adjustment of sample sizes and trial lengths accordingly.

The normalized prognostic index (PIN) score is an objective risk measure of prodromal signs and genetically estimated proximity to clinical diagnosis.[11] Higher PIN scores in a preHD population predict faster, more predictable progression, and thus larger effect sizes, for common HD clinical trial outcomes.[6] Therefore, it provides an objective measure that can be used to stratify preHD individuals according to predicted rate of disease progression across various outcome measures. We propose that the use of a PIN score threshold could enable the inclusion of prodromal individuals in clinical trial populations and thereby provide a means to optimize the composition of the study sample while minimizing the impact on statistical power and increase in required study size or length.The present study builds on our previous analyses[6] and explores the use of a screening PIN score for enabling the inclusion of prodromal individuals in clinical trials intending to enroll a perimanifest population. We assess relevant parameters, including trial duration, composition of a screening pool, and effects of PIN-defined preHD/HD compositions on outcome measures and sample sizes.

Patients and Methods

Data Source

Retrospective analyses were performed on the December 2018 data cut of ENROLL-HD (NCT01574053). ENROLL-HD is a global platform designed to facilitate clinical research in HD[12] and includes centers across Europe, Australasia, and the Americas that combine populations from the previous REGISTRY[13] and Cooperative Huntington's Observational Research Trial[14] studies with additional sites. Data sets for 10 core assessments are collected annually from all research participants as part of this multicenter, prospective, observational longitudinal registry study. Participants in the December 2018 data cut were enrolled between July 2012 and October 2018. The study was approved by the human subjects ethics boards of all participating institutions. The data used here were provided by the CHDI foundation (the ENROLL-HD study sponsor) after anonymization.

A total of 3557 participants with preHD, 2269 participants with stage 1 HD, and 2662 participants with stage 2 HD were included in the analyses. The total sample of preHD participants reflects the exclusion of 408 preHD participants with total motor score (TMS) >20 or TFC <11 (these participants would be considered to have been diagnosed with HD by many clinicians). Individual participant data with approximately annual follow-up were available. Most follow-up visits occurred ±2 months from the targeted annual follow-up date. Visits occasionally occurred up to 6 months after the targeted date. Analyses were performed using a maximum of 3.5 years of follow-up data per participant to approximate typical clinical trial time frames.

Calculation of PIN Scores and Diagnosis Rates

PIN score calculations and application of PIN score thresholds were performed as described previously.[6] Baseline PIN scores for each participant were calculated from the number of CAG trinucleotide repeats, age, TMS, and

Symbol Digit Modalities Test score.[11] PIN score thresholds of 0.0 and 0.4 were chosen to represent the approximate top 40% and top quartile of risk within ENROLL-HD (40.1% and 26.3%, respectively).[6,11]

Cumulative clinical diagnosis rates at the 2- and 3-year follow-up visits were calculated using Kaplan–Meier survival statistics and are summarized descriptively. This standard statistical method provides a slightly different estimate than direct enumeration of those who have remained in the study for the required period in that it adjusts for the rate of participants lost to follow-up (censored) for reasons presumed unrelated to diagnosis onset.

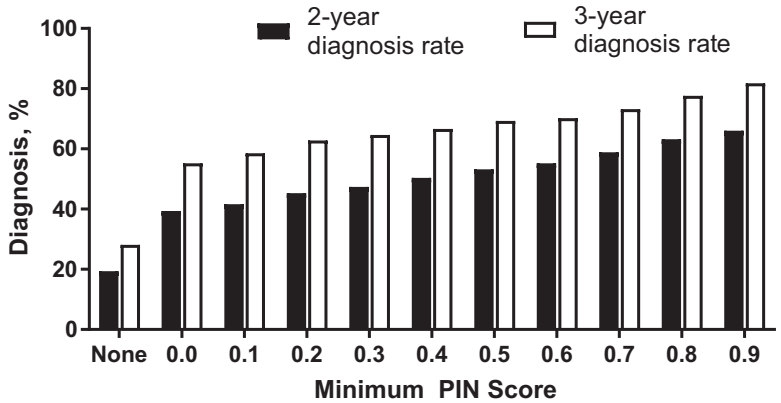
Application of PIN Thresholds to Hypothetical Clinical Trial Populations

The ratio of preHD to early HD applicants within a clinical trial pool is difficult to predict and may not match the ratio observed in ENROLL-HD. Thus, the potential proportions of prodromal participants meeting PIN criteria for inclusion were estimated in three steps: (1) within the ENROLL-HD data, we recorded the observed proportion of preHD that surpassed various proposed PIN thresholds; (2) we assumed various proportions of total preHD, regardless of PIN score (ie, 30%, 40%, 50%, or 65%), within future screening samples; and (3) the proportions exceeding PIN cutoffs from step 1 were then rescaled by the proportions of total preHD assumed in step 2.

Longitudinal Effect Size Modeling and Sample Size Estimation

Longitudinal effect size modeling and subsequent sample size estimation were based on longitudinal random effects models with correlated intercepts and slopes. Length of follow-up, treated as a continuous linear effect, was the only fixed-effect predictor variable. All available observations from participants in the group of interest were used, including from participants with only a baseline measure. This approach retained robustness of model estimates against bias due to study dropout or uneven follow-up length. Treatment effect size was defined as the difference in net predicted change from baseline over time divided by the subject-to-subject variation (standard deviation) around that mean change, estimated from the random slope effect and residual variances within the models. Effect size was used to translate fitted model results to projected future sample sizes using the well-known formula for *t* statistics.

Sample size estimates are the *combined* total for equally sized treatment and placebo groups. Sample size calculations were based on the following assumptions: 50% slowing of the disease progression effect size (longitudinal rate of change) relative to placebo, type I error of 5%, and type II error of 20%. Calculations are first-order approximations based on simple assumptions of equally sized treatment and placebo groups, no study dropouts, and an analysis based only on the net change from baseline to the end of the study. For the various hypothetical mixture ratios of preHD and combined stages 1 and 2, sample size was estimated by weighting the log-likelihood contributed per subject in separate longitudinal models of the preHD and the combined stage 1 and 2 data (see supplementary methods for further estimation details). For the potential outcome measures discussed, ENROLL-HD natural-history effect sizes are very similar in HD stages 1 and 2, and sample size estimates are nearly invariant to the assumed mixture of the stages. We therefore used



Minimum PIN Score	None	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
ENROLL-HD preHD sample, %	100	40.1	37.2	33.1	29.9	26.3	23.3	20.9	18.2	15.9	13.9
2-year diagnosis rate, %	19.4	39.4	41.6	45.3	47.4	50.4	53.2	55.2	58.9	63.2	66.0
3-year diagnosis rate, %	28.1	55.2	58.5	62.8	64.6	66.6	69.3	70.2	73.2	77.6	81.8

FIG. 1. PIN scores ≥0.0 are associated with higher rates of new motor diagnoses. Rates of new motor diagnoses approximately double among those with PIN scores of 0.0 or higher compared to the entire preHD group of ENROLL-HD participants. preHD, prediagnosis Huntington's disease; PIN, prognostic index.

TABLE 1 *Theoretical PIN-stratified participant composition for various preHD screening pool percentages*

Prevalence preHD in screening pool*	PIN cutoff	preHD (%)	Stage 1 (%)	Stage 2 (%)
0.30	0.0	13.6	39.9	46.5
0.30	0.4	9.4	41.4	49.3
0.30	1.0	4.5	42.5	53.0
0.40	0.0	19.7	37.1	43.2
0.40	0.4	13.9	39.3	46.8
0.40	1.0	6.8	41.4	51.8
0.50	0.0	26.8	33.8	39.4
0.50	0.4	19.5	36.8	43.8
0.50	1.0	9.9	40.1	50.0
0.65	0.0	40.5	27.5	32.0
0.65	0.4	31.0	31.5	37.5
0.65	1.0	16.9	36.9	46.1

*Within ENROLL-HD preHD accounts for approximately 40% of the candidate pool.
preHD, prediagnosis Huntington's disease; PIN, prognostic index.

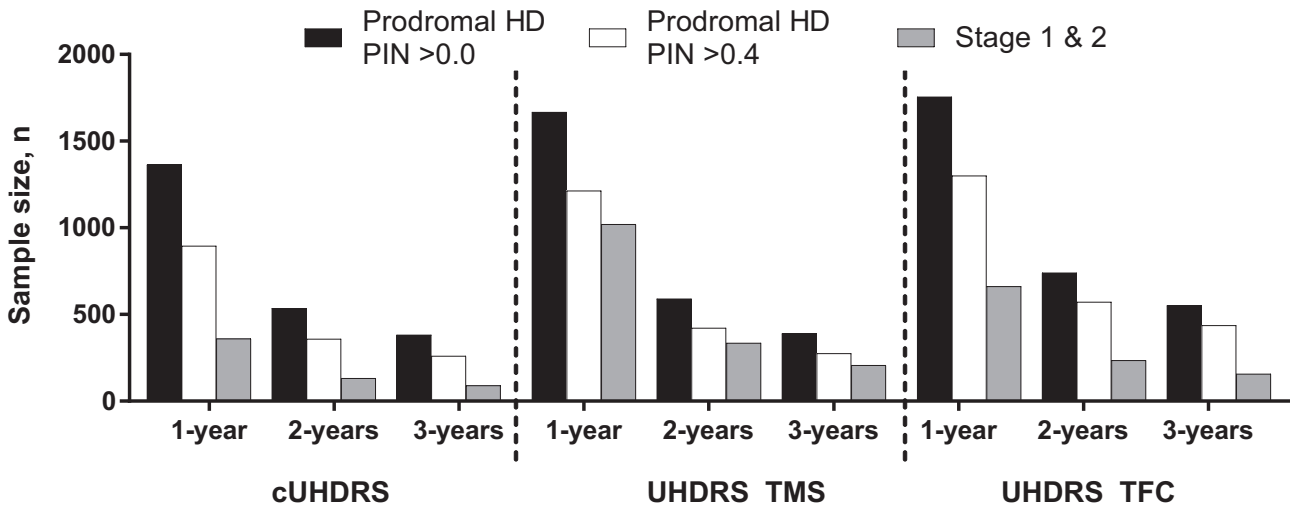


FIG. 2. Separate sample size estimates for prodromal HD, PIN cutoff >0.0 or >0.4, and HD stages 1 and 2, based on length of follow-up, and instrument: cUHDRS, UHDRS TMS, and UHDRS TFC. cUHDRS, composite Unified Huntington's Disease Rating Scale; HD, Huntington's disease; PIN, prognostic index; TFC, total functional capacity; TMS, total motor score; UHDRS, Unified Huntington's Disease Rating Scale.

the observed stage 1 and 2 mixture in ENROLL-HD for our calculations.

Results

PIN Thresholds Capture Perimanifest Patients in ENROLL-HD

Roughly one quarter (26.3%) of ENROLL-HD participants with preHD had PIN scores of at least 0.4, and 40.1% had PIN scores of at least 0.0. As shown in Figure 1, the rates of new motor diagnoses approximately double among those with PIN scores of 0.0 or higher compared to the entire preHD group of ENROLL-HD participants. Two- and 3-year clinical diagnosis rates of HD were 39.4% and 55.2%, respectively, for PIN >0.0 (Fig. 1). Retrospectively, the baseline PIN threshold of 0.0 was met by 81.4% of new diagnoses after 2 years and 78.8% of new diagnoses after 3 years. Simply stated, the 40% at highest baseline

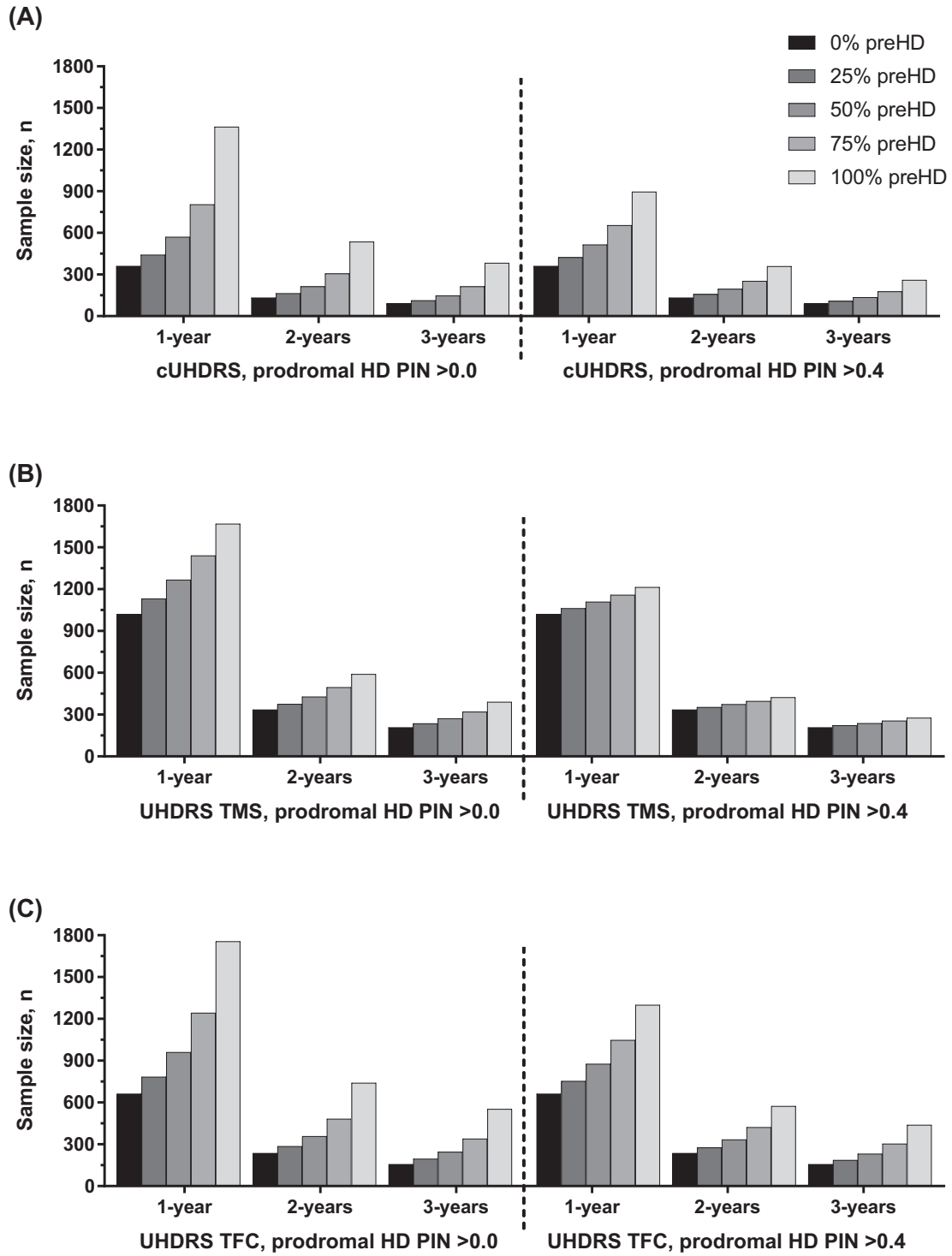


FIG. 3. Sample size estimates according to percentage prodromal HD, PIN cutoff >0.0 or >0.4, length of follow-up, and instrument: (**A**) cUHDRS, (**B**) UHDRS TMS, and (**C**) UHDRS TFC. cUHDRS, composite Unified Huntington's Disease Rating Scale; HD, Huntington's disease; preHD, prediagnosis Huntington's disease; PIN, prognostic index; TFC, total functional capacity; TMS, total motor score.

risk (PIN >0.0) account for 81% of those who had progressed to diagnosis at 2 years. The 26% with PIN >0.4 account for 68.3% of diagnoses within 2 years and 62.3% of new diagnoses within 3 years. Among ENROLL participants classified as diagnosed stage 1 or 2 at baseline, only 1.0% had PIN less than 0.0 and 2.4% had PIN less than 0.4. Thus, either of these thresholds captures nearly all who are in the categories recruited for most previous HD trials.

Effects of Adjusting PIN Threshold on Sample Size

If the entry criterion for a future trial was solely a PIN threshold (regardless of other elements of clinical status), sample sizes required for statistical power would nonetheless be sensitive to the proportion of prodromal participants enrolled. This would, in turn, depend in part on the distribution of clinical status and PIN scores among those being screened. Anticipating the proportion of preHD versus early-manifest HD that might be screened is difficult. The proportion may differ from that in the ENROLL-HD database, where preHD constituted 41.9% of the combined preHD, stage 1, and stage 2 pool. Assuming that preHD PIN scores in the population screened for clinical trial enrollment were distributed similarly to preHD in ENROLL-HD, the expected final proportion of prodromal HD enrollees in a trial can be calculated based on PIN threshold and the proportion of preHD within the screening pool (Table 1). If the prodromal proportion enrolled is to be limited to, for example, 25%, an appropriate final choice of PIN cutoff will depend, in part, on a reasonably accurate estimate of the initial preHD prevalence among those being screened.

Effects of Proportion of Prodromal Participants, Length of Follow-Up, and Outcome Measures on Required Sample Size

We explored the implications of enrolling prodromal participants on sample size requirements. In ENROLL-HD, estimated sample sizes for a continuous perimanifest trial (combined prodromal and stage 1 or 2 participants) vary depending on the minimum PIN score, ratio of prodromal to combined stages 1 and 2 in the participant sample, length of follow-up (1, 2, or 3 years), and the outcome utilized (TMS, TFC, or composite Unified Huntington's Disease Rating Scale [cUHDRS]).

Separate sample size estimates for three groups are presented in Figure 2 (Supplementary Table 1 in Appendix S1): prodromal with PIN scores >0.0, prodromal with PIN scores >0.4, and combined stage 1- and 2-diagnosed HD. Results for varying mixtures of these groups according to the PIN threshold and percentage prodromal in a combined perimanifest sample are presented in Figure 3 (Supplementary Table 2 in Appendix S1). The proportion of prodromal participants included within a trial has a large effect on required sample sizes, especially if cUHDRS or TFC are used as outcomes. However, a higher PIN score threshold limits the numbers of preHD subjects and increases the proportion of those with preHD who are truly prodromal and contribute more to efficacy outcomes compared to those who are farther from onset.

Discussion

In this analysis, we used various PIN screening thresholds to model the inclusion of preHD individuals who are likely to be prodromal in a clinical trial population. Inclusion of such participants significantly enlarges the population of potential participants for HD clinical trials. It also enables the inclusion of participants who are earlier in their disease course and who may therefore respond more readily to disease-modifying therapies—even though this response may be more difficult to measure. Patient populations inclusive of prodromal subjects may be especially salient for experimental cell or gene therapies applied directly to the basal ganglia because these tissues are already highly compromised and atrophic by stage 1.

Applying the PIN score to clinical trial design and enrollment has several advantages. It enables researchers to define the perimanifest population using adjustable, probabilistic boundaries rather than with descriptive and subjective constructs like "later prodromal," subtle prodromal signs and symptoms, or clinical diagnosis, which can be imprecise and subject to bias, especially when applied as trial entry criteria. In particular, using a PIN threshold allows for a continuum of disease in the trial population and for the estimation of the required number of trial participants, depending on the selected outcome measure. Nearly all who are currently defined as diagnosed with stage 1 or 2 disease would also be captured using only the proposed PIN thresholds. Therefore, a PIN threshold that will allow for the inclusion of prodromal individuals who are likely to progress rapidly without excluding stage 1 or 2 individuals can be selected. A PIN threshold might also be adjusted adaptively during a trial as a means of attaining a desired composition.

Previous analyses demonstrated that a PIN score can be effectively employed to enrich preHD participant selection for those most likely to experience measurable decline, and this enrichment substantially reduces the required sample sizes for clinical trials enrolling only preHD individuals.[6] The current analysis extended these findings to address whether PIN thresholds can be effectively used as screening criteria to select for a specific proportional composition of participants with prodromal and early-manifest HD. We estimate the effect of this proportional mix on the expected progression rates and required sample sizes, which vary depending on outcome measure and trial duration. Real-world sample size estimates would require further adjustment based on design decisions such as frequency of intermediate follow-up, minimum anticipated treatment effect, and rates of follow-up loss. However, the *proportional* effect of PIN-based screening on sample sizes would change little, if at all, by these refined

considerations.[6] Our estimates of the relationship between trial length and statistical power are inconsistent with those predicted by most textbook formulae for longitudinal sample size. Those methods assume only a random intercept per participant. This implies a constant standard deviation among participant scores over time, in which case ratios of sample size from 1 to 2 to 3 years would be 1, 1:4, and 1:9, respectively. In reality, interparticipant variability tends to increase with longer follow-up. This is captured by the random slope effect in our analysis models and its correlation with the random intercept. Consequently, the sample size decrease with longer follow-up, although notable, does not approach the dramatic efficiency predicted by commonly used but oversimplified statistical models.

Our estimates of PIN-stratified composition of trial participants were calculated using assumptions based on the ENROLL-HD patient sample. The composition of ENROLL-HD may differ from future trial screening populations. Thus, instead of accepting our precise sample size estimates uncritically, our assumptions should be reviewed and modified if appropriate. Regardless of assumption details (within a plausible range), these longitudinal analyses demonstrate that preselected PIN thresholds are an effective measure of screening for a perimanifest sample with measurable untreated disease progression, which is required for feasible trial sample sizes. This approach will facilitate the evaluation of potential disease-modifying therapies within the prodromal subset of the preHD population.

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Data Availability Statement

The data used in these analyses were provided by the CHDI Foundation, Inc. (the ENROLL-HD sponsor) after anonymization. ENROLL-HD is a clinical research platform and longitudinal observational study for Huntington's disease families intended to accelerate progress towards therapeutics. To accelerate HD therapeutic research & development, the Enroll-HD clinical research platform provides any verified researcher access to high-quality datasets and biosamples from the following HD clinical research studies: Enroll-HD, HDClarity, and TRACK-HD/Track-On HD. Data and biosamples can be accessed at https://enroll-hd.org/for-researchers/access-data/.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.