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Preparing for Preventive Clinical Trials: The Predict-HD Study
[Original Contribution]

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Abstract

Background: The optimal design and outcome measures for preventive clinical trials in neurodegenerative diseases are unknown.

Objective: To examine measures that may be associated with disease in the largest cohort ever recruited of prediagnosed individuals carrying the gene expansion for Huntington disease (HD).

Design: The Predict-HD study is a multicenter observational research study in progress at 17 sites in the United States, 4 in Canada, and 3 in Australia.

Setting: Genetics and HD outpatient clinics.

Participants: Five hundred five at-risk individuals who had previously undergone elective DNA analyses for the CAG expansion in the HD gene (predictive testing) and did not currently have a clinical diagnosis of HD.

Main Outcome Measures: Basal ganglia volumes on magnetic resonance images, estimated probability of diagnosis (based on CAG repeat length), performances on 21 standardized cognitive tasks, total scores on 3 scales of psychiatric distress, and motor diagnosis based on the Unified Huntington's Disease Rating Scale.

Results: Several variables showed progressive decline as the diagnostic ratings advanced toward manifest disease. Estimated probability of diagnosis was associated with Unified Huntington's Disease Rating Scale prediagnostic stages and varied from 15% in persons with no motor abnormalities to nearly 40% in those with abnormalities suggestive of probable disease. Striatal volumes, cognitive performances, and even psychiatric ratings declined significantly with motor manifestations of disease.

Conclusions: The documentation of biological and refined clinical markers suggests several clinical end points for preventive clinical trials. Longitudinal study is critical to further validate possible markers for prediagnosed HD.

PUBLICATION OF THE HUMAN genome [1] has fueled speculation on the future practice of medicine. It has been suggested that continuing advances in genetics and technology will dramatically accelerate the long-sought paradigm shift from treatment after diagnosis of human disease to the prediction and prevention of disease in healthy persons. However, experience to date with Huntington disease (HD), an autosomal dominant case in which the primary disease-causing gene has been known for more than a decade, [2] illustrates that the identification of disease genes is only the first step in a series of advances needed to prepare for preventive clinical trials in neurodegenerative disease.

Most treatments in adult-onset diseases are initiated with diagnosis, whereas improved genetic prediction should lead to prevention, or at least delayed onset and slowed progression, by allowing intervention at earlier stages in disease development. Early intervention with prophylactic treatment for people at risk for HD will only become possible once we have developed biological and refined clinical markers of the disease process in genetically identified individuals who have not yet been diagnosed as having HD. Our conceptual model for a preventive clinical trial is depicted in Figure 1, which shows how a putative prophylactic agent could be administered before significant decline in a given marker. The gentle slope of the upper line in this figure represents the more gradual rate of disease progression associated with prophylaxis, which successfully maintains the marker within the reference range longer. In contrast, the steeper line in Figure 1 depicts more rapid decline of the marker and symbolizes the earlier clinical diagnosis of an untreated individual. The personal, social, and financial benefits of earlier intervention are numerous.
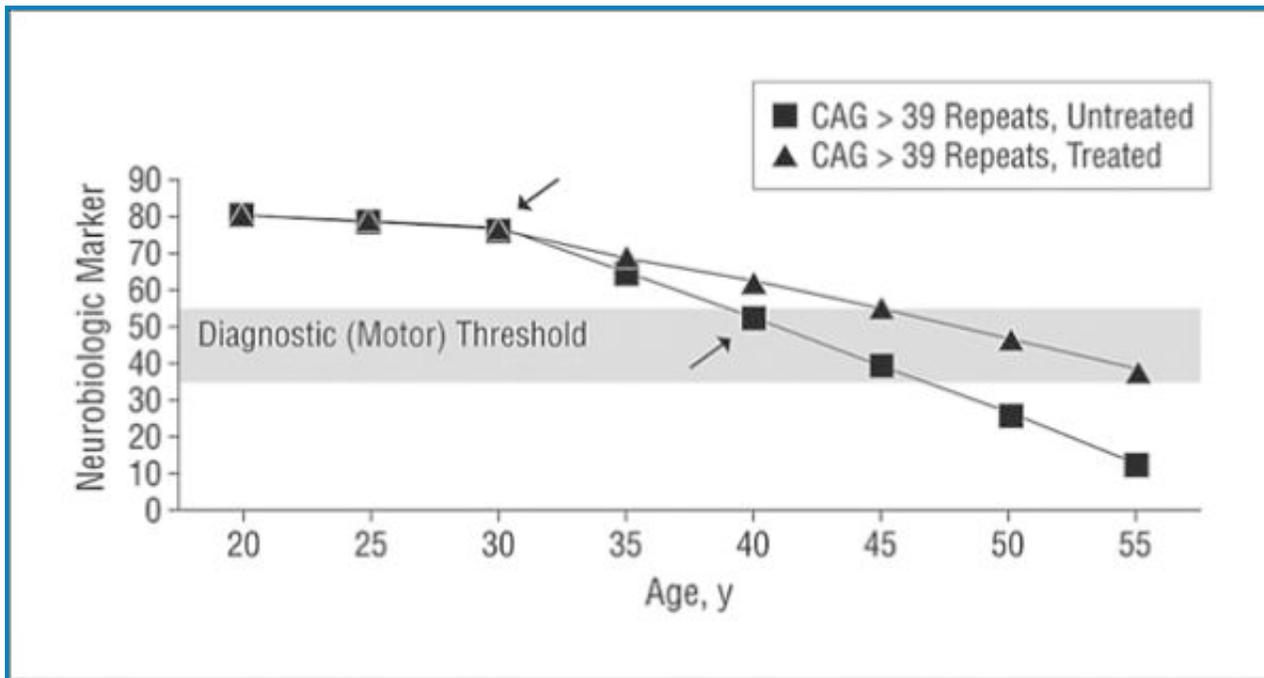
Figure 1. Intervention model for adult-onset disease. Downward-pointing arrow indicates administration of an effective prophylactic neuroprotective agent in a treated individual; upward-pointing arrow, clinical diagnosis of an untreated individual.

Predict-HD is a multisite, longitudinal, observational study aimed at identifying biological and refined clinical markers of early disease in humans and then validating the optimal markers and clinical end points for use in preventive clinical trials. The focus of this first report of the data from the Predict-HD study is to examine whether biological and refined clinical measures are associated with subtle motor signs detected by neurologists before clinical diagnosis.

In the absence of reliable means of quantifying disease-related changes before the diagnosis of HD, definitive efficacy trials initiated in prediagnosed individuals would necessarily be based on manifest disease onset. Such a study could take decades to complete because conclusions could be made only after a substantial portion of the sample had experienced clinical diagnosis. In contrast, a research study using well-characterized markers would allow clinical trials to be initiated many years before traditional disease diagnosis because potential efficacy could then be judged by reduction in the rate of marker decline rather than waiting for diagnosis. Thus, determination of the efficacy of interventions in prediagnosed HD can become possible only once so-called preclinical end points are defined.

Generally, high-risk individuals for specific illnesses have been identified using 3 primary tools: (1) measurement of subtle characteristics of disease-defining signs (eg, mild cognitive impairment as an early indicator of Alzheimer disease), (2) detection of established risk factors for disease (eg, high blood pressure as a risk factor for stroke), and (3) determination of increased genetic risk from family history or specific DNA properties (eg, apolipoprotein E and *parkin*). Huntington disease is a particularly useful model for identifying high-risk individuals for prediagnosis intervention because it is possible to know with near certainty, through a genetic test, who will one day develop the disease (using tool 3). In addition, risk factors for probability of earlier onset have been established using the length of the polyglutamine repeat [3] and modifying genes [4,5] (using a combination of tools 2 and 3). The aim of the Predict-HD study is to develop better tools for measuring subtle characteristics of disease-defining signs (tool 1) and to improve on the predictive ability and sensitivity afforded by tools 2 and 3. Ultimately, a combination of these 3 tools will be used to evaluate the efficacy of preventive clinical trials.

METHODS
PROCEDURE

Participants were recruited at 17 sites in the United States, 4 in Canada, and 3 in Australia as part of the National

Institute of Neurological Disorders and Stroke–supported Predict-HD study (for site list, see Appendix C, available from Dr Paulsen). All the sites were reviewed by appropriate governing boards, and all the participants signed a consent form that allowed de-identified research data to be sent to collaborative institutions for analyses. Data flow is diagrammed in Figure 2. Briefly, each site sent neuropsychologic data to Indiana University at Bloomington for double-scoring, mailed blood samples to Harvard University for DNA analyses, and dispatched magnetic resonance images (MRIs) to the University of Washington for striatal volumetric assessments. General case report forms were forwarded to the Clinical Trials Coordination Center at the University of Rochester, where all data were collated and missing data were queried. Data sets were sent to the University of Iowa, where data were cleaned, combined, and prepared for hypothesis testing.
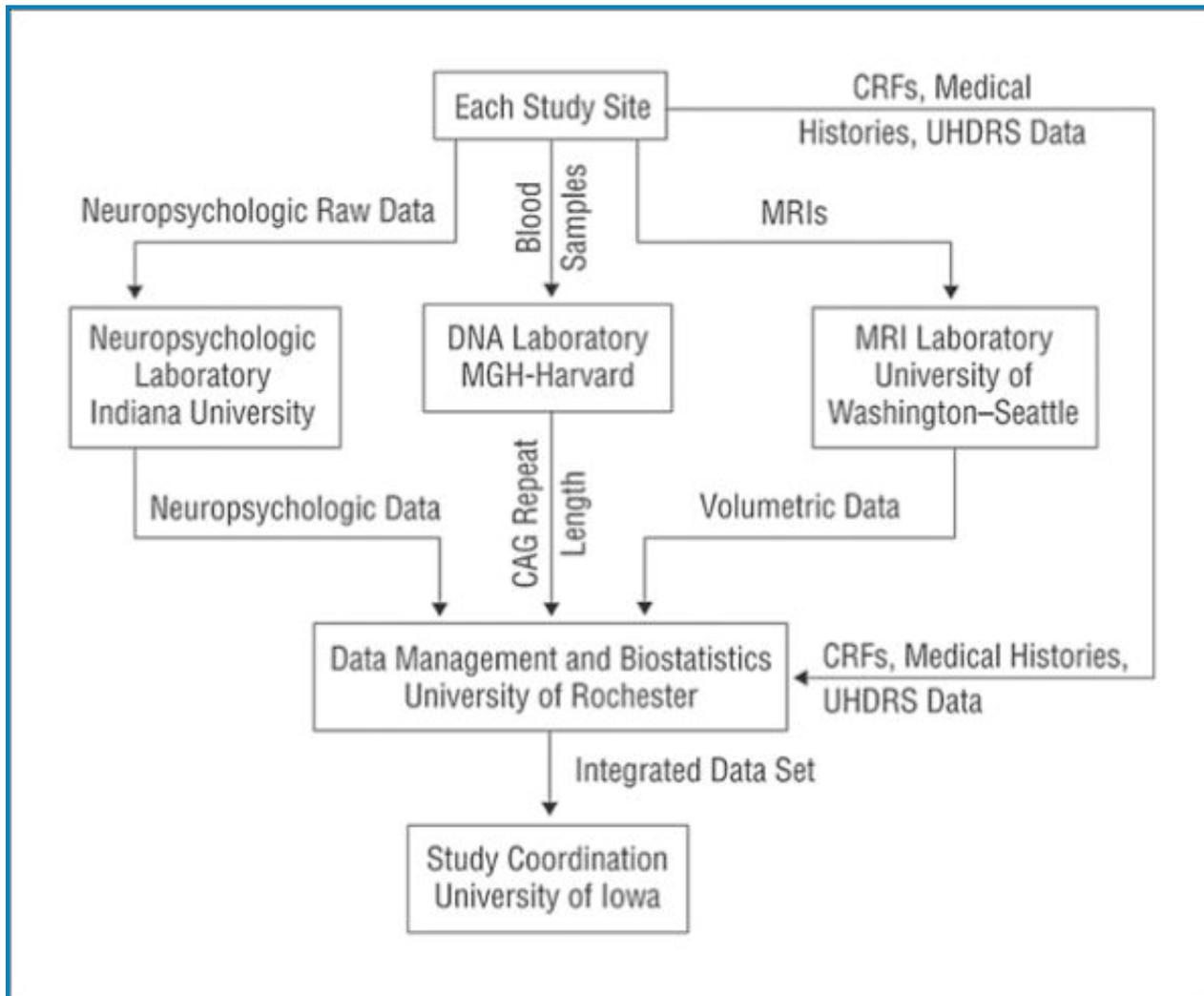
Figure 2. Data flow of the multisite Predict-HD study. CRF indicates case report forms; MGH, Massachusetts General Hospital; MRI, magnetic resonance imaging; UHDRS, Unified Huntington's Disease Rating Scale.

PARTICIPANTS

The present article is based on the first 17 months of study enrollment. Data for 505 participants were available for analysis. Inclusion criteria required that all the participants had undergone predictive testing based on having a family history of HD. To ascertain a comparison cohort, sites were asked to enroll 1 participant with a CAG repeat length in the reference range (eg, <30 repeats) for every 6 participants enrolled with a CAG repeat length in the HD range (ie, >=39 repeats). Exclusion criteria consisted of (1) evidence of unstable illness, (2) alcohol or other drug abuse, (3) a history of special education, (4) a history of other central nervous system disease or events, (5) pacemaker or metallic implants, (6) younger

than 26 years, (7) prescribed antipsychotic medications in the past 6 months, and (8) use of phenothiazine-derivative antiemetic medications for at least 3 months. Other prescribed, over-the-counter, and natural remedies were not restricted. Although the intent was to enroll only participants who were prediagnosed, provisions were made to enroll the few otherwise eligible individuals who seemed to be having HD symptoms if those individuals had not been diagnosed as having HD and considered themselves to be unaffected to avoid disclosing a diagnosis or suspected diagnosis of HD in the research setting.

MEASURES
HD Diagnostic Confidence Rating

Although HD is a disease composed of a triad of clinical symptoms (motor, cognitive, and psychiatric), its diagnosis has historically relied on the emergence of chorea. Diagnosis was defined using the final item of the Motor Assessment section of the Unified Huntington's Disease Rating Scale, [6] which queries, "To what degree are you confident that this participant meets the operational definition of the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder (eg, chorea, dystonia, bradykinesia, and rigidity) in a participant at risk for HD?" After completing the 15-item motor assessment, a movement disorder specialist responds to the diagnostic confidence question just mentioned using the following options: 0 indicates normal (no abnormalities); 1, nonspecific motor abnormalities (<50% confidence); 2, motor abnormalities that may be signs of HD (50%–89% confidence); 3, motor abnormalities that are likely signs of HD (90%–98% confidence); and 4, motor abnormalities that are unequivocal signs of HD (>=99% confidence). For the Predict-HD study, participants with a rating of 4 were considered "diagnosed" as having HD. Reliability studies conducted with 75 movement disorder specialists demonstrated adequate interrater reliability (weighted [kappa], 0.67; SE, 0.09) for HD diagnosis based on this scale. [7]

CAG Repeat Length

Huntington disease CAG genotyping was conducted as described by Warner et al. [8] Briefly, HD-specific oligonucleotide primers, flanking the HD CAG repeat, were used to specifically amplify the HD CAG repeat from template DNA samples in a polymerase chain reaction. The resultant radiolabeled HD-specific polymerase chain reaction products were displayed on a DNA sequencing gel format, exposed to x-ray film, and determined in number relative to that of known sequenced HD product "standards." A Huntington Study Group–conducted study [7] of interlaboratory variability of CAG length in HD demonstrated that reliability of CAG reports was very high ($r = 0.97$ for expanded alleles and $r = 0.99$ for normal alleles).

Estimated Probability of Diagnosis

Predicted age at motor symptom onset was estimated using a survival analysis regression equation based on CAG repeat length. Age-conditional expectations of time to onset were derived from this equation by 3 of us (J.S.P., M.H., and D.R.L.) using the largest cohort of patients with HD analyzed to date (2913 individuals from 40 centers worldwide; available at http://www.cmmt.ubc.ca/clinical/hayden). [3] We used this equation in the Predict-HD study to estimate the probability of diagnosis in the next 5 years for each participant given their current age and CAG repeat length.

MRI Measures

Image data for this project were obtained using a standard protocol designed to optimize visualization of the basal ganglia. In addition to a sagittal localizing series, we obtained an axial 3-dimensional volumetric spoiled gradient echo series, with a flip angle of 20°; echo time, 3 milliseconds; repetition time, 18 milliseconds; field of view, 24 cm; 124 slices at 1.5 mm per slice; matrix, 256 × 192; three-quarters phase field of view; and number of signals acquired, 2. Measurements were made by manually drawing the boundaries of the caudate and putamen, as described previously. [9,10] All the measurements were performed by a single rater after he established interrater reliability with 1 of us (E.A.) (intraclass correlation of 0.98 for the caudate and 0.99 for the putamen, based on 10 images).

Cognitive Assessment and Neuropsychiatric Measures

The cognitive assessment component of Predict-HD consists of a combination of clinical and experimental cognitive tests selected, on the basis of previous studies in animals and humans, to be sensitive to basal ganglia damage or HD. Six cognitive domains were targeted by the test battery: psychomotor speed, timing and movement sequencing, learning and memory, working memory, face and emotion recognition, and executive functions. All the study personnel who administered the cognitive battery underwent in-person formal training on the standardized test administration protocol and were required to meet performance criteria. All the data were double scored at the Indiana University Clinical Cognitive Neuroscience Laboratory (J.C.S.) (for the complete cognitive battery, see Appendix A, available from Dr Paulsen).

Psychiatric rating scales were administered to each participant in the study to screen for psychiatric distress and to better understand potential biological contributions to neuropsychiatric symptoms associated with brain disease (see Appendix B, available from Dr Paulsen).

RESULTS
DEMOGRAPHICS

Data suggest that this sample is highly similar to the general population in most demographic variables, although it is less ethnically diverse (97% vs 83% white) and slightly more educated (90% vs 84% high school graduates). Age of research participants ranged from 26 to 76 years (mean ± SD age, 42 ± 9.9 years), 89% were right handed, and 64% were women. Seventy percent of the participants were currently married, although 16% had undergone at least 1 divorce. The CAG repeat length was expanded in 452 of the first 505 participants enrolled (mean ± SD, 42.5 ± 2.4 repeats; range, 39–58 repeats). The remaining 53 participants had no CAG expansions in the HD gene and served as the comparison group. Thirteen percent of the participants reported having symptoms that concerned them as possibly being related to HD, and several were taking compounds believed to slow the disease, such as multivitamins (19%), vitamin E (15%), coenzyme Q10 (13%), eicosapentaenoic acid/fish oil (12%), vitamin C (9%), and creatine (5%).

GENETIC AND MOTOR CHARACTERISTICS

We compared the diagnostic confidence ratings for participants with vs without gene expansion. Eleven participants (2%) were diagnosed as having definite HD, and their data were excluded from further analysis. Twenty-four participants (5% of gene-expanded individuals) were rated as having "probable HD," whereas 15% (n = 69) were considered to have "possible HD." Most participants were rated as having minor (44%; n = 197) or no (33%; n = 151) motor signs. Sixty-two percent of the participants without gene expansion (n = 33) were considered to have no signs, 32% (n = 17) were found to have minor motor abnormalities that were not suggestive of HD ("soft signs"), and 6% (n = 3) were diagnosed as having possible HD. No participants without the gene expansion were diagnosed as having probable or definite HD.

MAGNETIC RESONANCE IMAGING

The MRI volumes of the striatum are shown in Table 1 by Unified Huntington's Disease Rating Scale diagnostic confidence groups. The average size of the striatum is largest in the group with a motor rating of 0 (mean = 17.06 cm^3) and becomes smaller as the diagnostic confidence rating, based on motor signs, increases (mean = 14.89 cm^3).

Table 1. Diagnostic Confidence Distributions by Total Motor Score, Reported CAG Repeat Length, Probability of Disease Onset in the Next 5 Years, and Striatum Volume for Individuals With the Gene Mutation*

Diagnostic Confidence Level	Motor Score	CAG Repeats	5-y Probability	Striatum Volume, cm^2
0 = no signs	1.20 (1.66)	42.23 (2.22)	0.15 (0.13)	17.06 (2.68)
1 = soft signs	5.80 (3.47)	42.47 (2.17)	0.21 (0.17)	16.46 (3.13)
2 = possible HD	10.26 (4.40)	42.54 (2.65)	0.28 (0.20)	15.88 (2.39)
3 = probable HD	16.92 (7.72)	44.33 (4.01)	0.39 (0.16)	14.89 (2.76)

Abbreviation: HD, Huntington disease.
*Data are given as mean (SD). $P < .001$ for all (2-sided tests of increasing or decreasing means across categories). See the "Methods" section for details.

Table 1. Diagnostic Confidence Distributions by Total Motor Score, Reported CAG Repeat Length, Probability of Disease Onset in the Next 5 Years, and Striatum Volume for Individuals With the Gene Mutation[*]

COGNITIVE PERFORMANCE AND PSYCHIATRIC CHARACTERISTICS

Overall, higher diagnostic confidence ratings were associated with poorer cognitive performances (Table 2). Psychiatric test scores are given in Table 3. For every measure, the mean distress level of the participants with HD gene expansion was greater than that in the comparison group without HD gene expansion, and levels of distress were positively associated with the diagnostic confidence level.

Table 2. Cognitive Performance by Diagnostic Confidence*

Cognitive Task	Diagnostic Confidence Level					ANOVA P Value
	Gene Negative (n = 53)	0 (n = 151)	1 (n = 197)	2 (n = 69)	3 (n = 24)	
Psychomotor speed						
Symbol Digit Modalities Test (maximum = 110)†	55.81 (8.45)	56.63 (10.86)	50.10 (10.85)	48.02 (9.30)	42.60 (10.99)	<.001
Trail Making Test–Part A‡	24.05 (8.12)	24.41 (8.03)	26.99 (8.98)	28.72 (9.18)	35.10 (10.99)	<.001
Speeded Tapping–Thumbs, mean good responses	256.18 (32.71)	244.44 (36.37)	277.17 (42.06)	219.56 (50.90)	200.80 (48.80)	<.001
Simple Response Task, movement times, ms	202.60 (62.50)	213.54 (63.25)	242.33 (87.65)	243.90 (74.41)	262.55 (59.20)	<.001
2-Choice Response Task, movement times, ms	239.68 (56.95)	250.02 (75.30)	275.45 (86.80)	295.17 (100.36)	295.17 (74.85)	<.001
Timing and movement sequencing						
Tone Tapping–Thumbs, variability, ms	40.82 (14.01)	44.31 (16.53)	50.49 (18.39)	56.99 (22.46)	63.18 (18.77)	<.001
Buttons Task–Block 3, movement times, ms	310.02 (47.59)	319.37 (61.23)	334.55 (68.79)	347.53 (72.42)	367.19 (76.94)	<.001
Learning and memory						
HVLT Total Learning, sum of trials 1-3 (maximum = 36)	28.76 (3.75)	27.57 (4.44)	26.03 (4.94)	24.34 (5.40)	22.33 (5.26)	<.001
HVLT Delayed Recall (maximum = 12)	10.26 (1.91)	10.04 (2.05)	9.38 (2.20)	8.61 (2.55)	8.46 (2.15)	<.001
Serial Response Task—Block 4, response times, ms	412.06 (63.57)	413.75 (73.65)	462.17 (112.97)	485.88 (97.99)	507.37 (90.70)	<.001
Working memory						
Letter-Number Sequencing (maximum = 21)†	12.73 (2.98)	12.32 (2.70)	11.45 (2.50)	10.60 (2.14)	11.15 (2.89)	<.001
Dual Verbal Working Memory Test (maximum = 11)†	5.23 (1.71)	5.29 (1.72)	4.77 (1.85)	4.29 (1.31)	4.15 (1.93)	<.001
Face and emotion recognition						
Benton Facial Recognition Test (maximum = 27)†	23.23 (2.08)	22.34 (1.90)	22.55 (1.97)	22.12 (2.11)	22.05 (2.01)	.001
Emotions Task–Static Version, disgust score (maximum = 10)	8.13 (1.48)	7.60 (1.94)	7.30 (2.04)	6.42 (2.25)	6.92 (2.21)	<.001
Emotions Task–Dynamic Version, disgust difference score (maximum = 8)§	0.61 (0.94)	0.79 (1.11)	0.80 (0.96)	0.85 (1.03)	0.63 (1.13)	.88
Executive functions						
Stroop Test–Interference†	47.49 (8.20)	47.10 (9.52)	44.10 (10.04)	41.78 (8.12)	38.17 (9.51)	<.001
Verbal Fluency Test, sum for 3 letters (BWR or LDT)†	45.30 (12.59)	42.98 (11.64)	40.63 (10.78)	38.09 (9.87)	38.52 (15.87)	<.001
Trail Making Test–Part B‡	57.49 (31.54)	57.20 (21.40)	69.43 (34.18)	71.82 (27.31)	76.94 (35.85)	<.001
Tower Task, 4-disk version, moves per 4 trials	99.70 (24.32)	102.68 (25.27)	110.63 (25.93)	110.21 (29.69)	113.67 (21.62)	<.001
Set-Shifting Task, total errors—extradimensional shift	6.17 (7.57)	8.05 (9.07)	10.33 (10.01)	10.90 (10.26)	10.38 (10.17)	<.001
Smell Identification Test (maximum = 40)†	34.93 (2.34)	33.75 (3.86)	33.86 (3.56)	31.98 (4.83)	31.58 (6.56)	<.001

Abbreviations: ANOVA, analysis of variance; BWR and LDT, letters given for verbal fluency; HVLT, Hopkins Verbal Learning Test.
*Data are given as mean (SD) unless otherwise indicated.
†Total correct.
‡Seconds to complete.
§Difference score = total correct for stimuli with movement minus total correct for stimuli without movement.

Table 2. Cognitive Performance by Diagnostic Confidence*

Table 3. Psychiatric Measures for Participants With Gene Mutation in Each Diagnostic Confidence Level and for Controls*

Measure SCL-90-R	Diagnostic Confidence Level					Anova P Value†
	Controls	0	1	2	3	
GSI	48.00 (8.82)	51.13 (9.60)	53.34 (12.15)	51.60 (10.97)	54.83 (10.22)	<.001
PST	48.49 (9.45)	51.52 (9.68)	53.06 (12.13)	51.38 (10.76)	53.89 (10.77)	<.001
PSDI	46.77 (7.11)	48.96 (7.63)	50.93 (9.54)	51.33 (8.70)	55.47 (6.98)	<.001
BDI-II	3.95 (5.17)	7.00 (7.79)	7.80 (8.53)	8.05 (9.34)	9.18 (7.39)	<.001
BHS	1.92 (2.43)	2.97 (2.97)	3.03 (3.11)	3.06 (3.08)	6.10 (4.20)	.02

Abbreviations: ANOVA, analysis of variance; BDI-II, Beck Depression Inventory II; BHS, Beck Hopelessness Scale; GSI, Global Severity Index; PST, Positive Symptom Total; PSDI, Positive Symptom Distress Index; SCL-90-R, Symptoms Checklist–90 Revised.
*Data are given as mean (SD) unless otherwise indicated.
†P values are for 2-sided tests of increasing or decreasing means across categories. See the "Methods" section for details.

Table 3. Psychiatric Measures for Participants With Gene Mutation in Each Diagnostic Confidence Level and for Controls[*]

COMMENT

Findings from this study suggest that genetic characteristics can be used to effectively recruit a research sample at increased risk for neurodegenerative disease. Comprehensive assessments of clinical, radiographic, cognitive, and psychiatric characteristics suggest robust evidence of deterioration on all measures with increasing confidence of clinical diagnosis. That is, subtle motor abnormalities, reduced brain volumes, cognitive impairments, and psychiatric distress seem to be significantly altered before traditional diagnosis of HD. Longitudinal research is necessary to refine these biological and clinical markers to establish preclinical end points that may be used in experimental therapeutics for the prevention of disease.

These findings confirm and extend findings from previous studies suggesting that subtle changes in motor function, speed of movement, and reaction time are present in HD gene–expanded carriers who do not exhibit definite choreiform movements and who do not have sufficient signs to make a clinical diagnosis of HD. Although conflicting results have been found regarding motor impairment and decline in individuals without definite chorea, [11–14] our findings provide strong support for a series of studies [15–18] showing subtle motor changes in prediagnosed HD. One study [19] found small, but significant, differences in physiologic measures of reaction time, movement time, and movement time with decision between at-risk participants with and without HD expansion. The current findings provide the best evidence to date of a robust progressive deterioration in motor abnormalities in the largest sample studied of participants with gene expansion. Follow-up evaluation will determine which motor abnormalities best predict conversion to manifest HD.

It is well accepted that significant basal ganglia volume loss is evident in persons at risk for HD before a clinical diagnosis is made. [9,20,21–23] The association of refined clinical measures with the basal ganglia volume loss, however, is less clear. Better definition of the changes occurring before and around diagnosis could facilitate future treatment trials, as it would allow selection of participants who are most likely to convert to the symptomatic stage of HD during the clinical trial. Findings from the present study show that volume loss is unequivocally associated with minor motor abnormalities before diagnosis of HD is warranted. Further research will establish whether volume loss and minor motor abnormalities are concurrent or additive predictors of imminent disease diagnosis.

Findings from the cognitive assessment indicate unmistakably that each higher increment on the motor ratings is associated with a decrement in cognitive performances. This trend was consistent and statistically significant throughout the entire set of tests included in the clinical battery. A test by test consideration of these findings, which is beyond the scope of the present study, is necessary to determine which tests show the largest effect sizes in this sample. Such follow-up and longitudinal analyses will help determine which cognitive markers of progression can then be added to MRI, motor, and neurochemical measures to best predict imminent diagnosis of HD.

Individuals with CAG expansion in the present study who did not display any motor signs were within the reference range on standard neuropsychologic tests, although increased variance in this subgroup suggests that some individuals are showing more cognitive impairments than others. With increasing diagnostic confidence levels, performance worsened across most measures, including the standard neuropsychologic tests and the computerized measures. Further research is needed to determine which, and whether, refined motor and cognitive measures are independently predictive of HD diagnosis.

Similar to other studies of patients with preclinical HD, [24] high rates of psychiatric symptoms were reported in the current sample. These symptoms, however, tended to be in the subclinical range and were lower than those reported by patients with manifest HD. [25] In this sample, the most prevalent psychiatric disturbance was depression, which is substantially higher than lifetime prevalence rates in community controls (eg, 5%–25%). Number of reported suicide attempts in this cohort (7%) was greater than that in community samples (3%–4%), [26] comparable with other presymptomatic studies (8%), [27] but fewer than for individuals with symptomatic HD (29%). [28,29] Given the high levels of depression described in this sample, it is not

surprising that nearly one third of the participants reported taking an antidepressant agent, which is higher than the number reported in other studies of preclinical individuals. This discrepancy might represent an increased awareness and monitoring of psychiatric symptoms during the preclinical phase and the recently increasing acceptance and use of antidepressant drugs in the general population. [30–32] The rate of alcohol abuse in the current sample (8%) occupies a middle ground between that in community samples (eg, 5%–8%) and symptomatic patients (17%). [33]

The findings reported herein represent the most robust evidence to date that subtle clinical abnormalities are evident and MRI volumes show decline before a clinical diagnosis of HD is made. Numerous early findings are confirmed and extended because the sample size reported is nearly 10 times that of other publications. Prediagnosis clinical end points will become clear in the next few years as longitudinal data are analyzed and preclinical treatment strategies are available. Findings from this study will make preventive clinical trials feasible. For instance, a 4-year trial to test whether a drug slows the progression of HD by 20% conducted today requires at least 3000 people who have undergone predictive testing and were found to have expansion. Careful documentation of these refined clinical and biological characteristics will reduce the necessary sample sizes for preventive clinical trials by at least 50%. The data gained are also vital to eventually designing trials to test whether therapies given long before the time of manifest disease can delay diagnosis or slow functional loss.

Identification of specific disease genes has begun to shift the practice of medicine toward earlier intervention. The present article shows that it is feasible to recruit a large sample of healthy individuals who have a gene mutation responsible for a future fatal disease. The Predict-HD study has successfully enrolled more than 500 persons at risk for HD from 24 sites throughout the United States, Canada, and Australia. Baseline findings from this large sample of persons with the gene expansion responsible for HD indicate that brain volume loss, cognitive impairment, and psychiatric distress is evident before a clinical diagnosis is given. Clinical trials of experimental therapeutics to slow, reverse, or halt disease progression during the earliest period of disease are on the horizon, and data accrued from the Predict-HD study will better refine the design of these trials.

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Preventive Medicine; Randomized Trials

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