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Challenges assessing clinical endpoints in early Huntington disease

Jane S. Paulsen, PhD^{1,2,*}, Chiachi Wang, MS¹, Kevin Duff, PhD¹, Roger Barker, PhD, MD³, Martha Nance, MD⁴, Leigh Beglinger, PhD¹, David Moser, PhD¹, Janet K. Williams, PhD⁵, Sheila Simpson, MD⁶, Douglas Langbehn, MD^{1,7}, Daniel P. van Kammen, MD, PhD⁸, and the PREDICT-HD Investigators of the Huntington Study Group

¹Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, IA, USA

²Department of Neurology, University of Iowa Carver College of Medicine, Iowa City, IA, USA

³Cambridge Center for Brain Repair, Cambridge, UK ⁴Department of Neurology, Park Nicollet Clinic, St. Louis Park, MN, USA ⁵College of Nursing, University of Iowa, Iowa City, IA, USA ⁶North of Scotland Clinical Genetics Service, Aberdeen, Scotland ⁷Department of Biostatistics, University of Iowa College of Public Health, Iowa City, IA, USA ⁸Advisor to the CHDI Foundation, CHDI Management, Inc., Princeton, NJ, USA

Abstract

The primary aim of this study was to evaluate the current accepted standard clinical endpoint for the earliest-studied HD participants likely to be recruited into clinical trials. Since the advent of genetic testing for HD, it is possible to identify gene carriers prior to the diagnosis of disease, which opens up the possibility of clinical trials of disease-modifying treatments in clinically asymptomatic persons. Current accepted standard clinical endpoints were examined as part of a multi-national, 32-site, longitudinal, observational study of 786 research participants currently in the HD prodrome (gene-positive but not clinically diagnosed). Clinical signs and symptoms were used to prospectively predict functional loss as assessed by current accepted standard endpoints over 8 years of follow up. Functional capacity measures were not sensitive for HD in the prodrome; over 88% scored at ceiling. Prospective evaluation revealed that the first functional loss was in their accustomed work. In a survival analysis, motor, cognitive, and psychiatric measures were all predictors of job change. To our knowledge, this is the first prospective study ever conducted on the emergence of functional loss secondary to brain disease. We conclude that future clinical trials designed for very early disease will require the development of new and more sensitive measures of real-life function.

Keywords

Huntington disease; UHDRS; prodromal HD; functional capacity; clinical endpoints

*Correspondence, proofs, and reprint requests to: Jane S. Paulsen, PhD University of Iowa College of Medicine, 305 MEB Iowa City, IA 52242-1000 Tel.: 319-353-4551 FAX: 319-353-4438 jane-paulsen@uiowa.edu.

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INTRODUCTION

Huntington disease (HD) is an autosomal dominant neurodegenerative disorder for which there is no cure. Although clinicians use a variety of treatments to address the symptoms,¹ the ultimate research goal is to develop treatments that prevent, modify the course, or reverse the disease. Since the advent of genetic testing for HD, it is possible to identify gene carriers at or before the earliest stages of neural degeneration and before functional decline. Although these individuals do not yet meet criteria for a diagnosis of HD, research findings have documented clinical and biological characteristics of disease about 15 years before expected diagnosis.² Consistent with other medical conditions, the earliest phase of a developing disease is referred to as the “prodrome.” The term comes from the Greek word, *prodromos*, which means “running ahead of.” Although cognitive, motor, sensory, physiological, and neuroimaging markers of early HD have been reported,³⁻⁵ these measures are currently not established outcome measures for clinical trials. The next critical step is the validation of these markers against a well-defined (non-surrogate) clinical endpoint. Although often overlooked, the identification of a clinical endpoint is among the most important components of clinical research. According to the Food and Drug Administration, clinical endpoints are the most credible characteristics used to interpret the results of randomized clinical trials and reflect how a patient feels, functions, or survives.⁶⁻⁷ A major challenge for neurodegenerative disorders has been the identification of clinical outcome measures that accurately track disease. Recently, research groups have critically reconsidered clinical outcome measures for Multiple Sclerosis,⁸ Alzheimer disease,⁹⁻¹⁰ Amyotrophic Lateral Sclerosis,¹¹ and Parkinson disease.¹²⁻¹³

Primary outcome measures used in clinical trials of patients with diagnosed HD typically involve a clinical symptom or sign (e.g., chorea) and a measure of everyday function. One of the most frequently used measures of function in HD is the Total Functional Capacity scale (TFC).¹⁴ Although previous reports of cases in the HD prodrome suggest that the TFC is not sensitive at the earliest stages of HD,¹⁵⁻¹⁶ it is unknown whether clinical endpoints from the TFC will be sensitive to changes in a large sample of prodromal HD. The purpose of the proposed study was to examine the TFC scale in a large, longitudinal study of prodromal HD participants. It was hypothesized that basic personal activities (e.g., grooming, household chores) would not be affected in this cohort but that higher level items (e.g., occupation, finances) would be.

METHODS

Participants

PREDICT-HD is a longitudinal observational study of persons who chose to undergo predictive testing for the CAG expansion in the HD gene but did not meet criteria for a diagnosis of HD. Participants were recruited from 32 sites in the United States, Canada, Australia, and Europe beginning in October 2002. Institutional review board approval was obtained at all study and data-processing sites. Informed consents were obtained in accordance with the Declaration of Helsinki, which allowed researchers to send de-identified data to collaborating institutions. All participants were required to have undergone independent genetic testing for the HD CAG expansion. Only participants found to have an expansion in the HD gene (CAG > 35) and not clinically diagnosed according to the diagnostic confidence level of the Unified Huntington Disease Rating Scale (UHDRS)¹⁷ were included in the current paper. The diagnostic confidence level ranges from 0 (normal) to 4 (unequivocal extrapyramidal signs of HD, ≥ 99% confidence of the examiner). Only participants with a rating less than 4 are considered to be in the HD prodrome. Seven hundred eighty-six participants met these criteria. All participants underwent detailed motor, cognitive, psychiatric, and functional evaluations annually as previously described.^{2, 5} The

HD prodrome sample was 63.36% female and 97.45% Caucasian, with an average age of 40.82 (18–76 years), and average education of 14.31 years (8–20 years). Participants averaged 2.83 years of follow up (1–6 years).

Measures

Functional Outcomes—The TFC¹⁴ is a 5-item clinician rating scale typically completed after a brief interview with a patient and/or collateral source. The TFC globally assesses occupation, finances, domestic chores, activities of daily living, and level of care, with scores on each item ranging from 0 to either 2 or 3 (e.g., Occupation: 0 = unable, 1 = marginal work only, 2 = reduced capacity for usual job, 3 = normal). The five items are summed to yield a TFC total score, which ranges from 0 to 13 with greater scores indicating higher functioning. The TFC has been partitioned into five stages that indicate levels of disease severity based on functional decline. TFC scores from 11–13 represent stage I (least severe); 7–10, stage II; 3–6, stage III; 1–2, stage IV; and score of 0 is stage V (most severe). The Functional Assessment Scale (FAS)¹⁸ is a 25-item yes/no questionnaire of tasks related to occupation (e.g., accustomed work, volunteer work), finances (e.g., cash transactions, financial management), activities of daily living (e.g., driving, hygiene), domestic chores (e.g., home maintenance, laundry), level of care (e.g., home or supervised care), and physical abilities (e.g., walking, getting out of bed, falls). FAS scores range from 0 to 25 with “yes” responses receiving 1 point each. Lower scores indicate greater functional impairment.

Depression—The Beck Depression Inventory (BDI-II)¹⁹ is a 21-item self-report rating scale of depressive symptoms, such as irritability, low mood, lack of interest in enjoyable activities, and fatigue. Since depression is known to present differently in HD relative to psychiatric samples, we conducted a factor analysis of the 21 items. Findings suggested a two-factor solution in our sample of prodromal HD, which we labeled BDI-mood (items 1–3, 5–10, 14) and BDI-energy (items 15, 16, 20, 21) factors. All analyses were conducted with these two factors, in which higher scores indicate more symptoms.

Cognitive Functioning—The Symbol Digit Modalities Test (SDMT)²⁰ measures the number of correct responses on a timed task of symbol to digit transcription and taps psychomotor speed, attention, and working memory. Higher scores indicate better cognitive functioning.

Motor Functioning—A movement disorder specialist examined the participants and rated the presence and severity of 15 individual motor signs (e.g., finger tapping, chorea, dysarthria) using the UHDRS.¹⁷ The sum of motor signs can range from 0 to 124 signs with higher scores indicating more impaired motor function.

Proximity to Diagnosis—Estimated years to diagnosis was calculated using a CAG- and current age-based predictive model developed from a worldwide sample of 2,913 individuals²¹ and validated with nearly 100 prospectively diagnosed patients from PREDICT-HD.^{2, 5, 22} Cases were considered “far” from diagnosis if estimated years were greater than 15, “mid” to diagnosis if their estimated years were 9–15, and “near” to diagnosis if estimated years were less than 9. These definitions correspond roughly to terciles of diagnostic proximity among PREDICT-HD participants.

Statistical Analyses

Linear Mixed Models with an unstructured covariance assumption utilized data from every visit to estimate the annual rate of change in TFC, FAS, BDI, SDMT, and motor scales. For the BDI energy factor, we instead used a full-rank Toeplitz covariance structure, due to

nonconvergence of the unconstrained covariance estimate.²³ To study predictors of longitudinally observed functional loss, we used multivariate survival analysis based on Cox proportional hazards models²⁴⁻²⁵ with the time to the loss of accustomed work as the outcome variable. BDI factor scores, SDMT, and total motor scores were the main predictor variables of interest in our statistical models, and the combination of these four were used in the multivariate models presented here. These predictor variables were measured at each visit, and we compared the results of survival models where the baseline values of these variables were used as risk predictors and models where these predictor values were updated at each visit prior to loss of accustomed work (i.e. fixed versus time-dependent predictor variables).²⁵ The consideration of both baseline and time-dependent predictors allowed us to evaluate the validity of the proportional hazards assumption in the Cox regression model. Cross sectional baseline associations between predictor variables and impairment on specific functional items were assessed via multivariate logistic regression.²⁶

RESULTS

The average TFC score was 12.81 out of a possible 13 (SD = 0.67) and the average FAS score was 24.83 out of a possible 25 (SD = 0.76), which were both near the ceiling scores (i.e., highest level of functioning) for these measures. Mean total score on the BDI-II was 8.09 (SD = 8.80), which is in the “minimally depressed” range. Performance on the SDMT was 49.98 (SD = 11.62), which falls in the “average” range (~36th percentile). The total motor score from the UHDRS was 4.95 (SD = 5.26), which suggests minimal motor abnormality. Proximity to estimated diagnosis had a group mean of 14.48 years (SD = 7.29), with 192 being “near” to diagnosis (estimated 7.00 years), 292 being “mid” to diagnosis (11.65 years), and 296 being “far” from diagnosis (22.12 years).

Eighty-nine percent of the prodromal HD participants were rated as having the maximum possible score on the TFC and 91% were at maximum on the FAS. Over 88% of the participants were rated as having the maximum score on both functional scales. Eight percent of the participants lost only one point on the TFC, the FAS, or both scales, and 2% lost only 2 points on either or both scales. An additional 1% lost 3 points on the TFC, the FAS, or both. In other words, over 99% of the prodromal HD sample scored over 10/13 on the TFC and 22/25 on the FAS.

TFC and FAS items most frequently endorsed at less than maximum levels are shown in Table 1. These suggest that questions about work and managing finances are the most common functional limitations reported in this sample of persons in the HD prodrome. On the FAS, the item most frequently lost was about whether participants could “engage in gainful employment in his/her accustomed work” (see Table 1). Sixty participants failed to endorse this item at baseline. Logistic regression was conducted to determine which clinical symptoms were associated with less than maximum capacity in accustomed work. Better scores on the SDMT cognitive score ($p = 0.0007$), the BDI-energy factor ($p < 0.0001$), and the UHDRS total motor score ($p = 0.0003$) were all significantly associated with participants currently working their accustomed job (see Table 2).

The annual rates of change for the two functional measures were -0.06 points/year (SE = 0.01) for the TFC and -0.07 (SE = 0.01) for the FAS. Rates of change for the BDI-II total was -0.11 /year (SE = 0.09) and 0.83 /year (SE = 0.08) for the total motor score. All of these change rates were statistically significant ($p < 0.0005$). Annual rates of change for all clinical variables are shown (Table 3) for each HD prodrome proximity group (near, mid, far). Functional and motor measures appear able to reflect significant change in near- and mid-to-diagnosis participants whereas the cognitive and behavioral measures are able to detect changes in the mid- and far-from-diagnosis participants.

Finally, there were 92 prodromal HD participants who initially denied functional loss on the “gainful employment in his/her accustomed work” item but eventually reported this functional loss during the study. Survival analysis of these data was conducted using predictors from each of the primary clinical symptoms/signs of HD: depression (i.e., BDI factor scores), cognition (i.e., SDMT) and motor signs (i.e., UHDRS total motor score). For 643 participants with complete data (89 of whom had a prospective loss of function), the energy factor of the BDI, the SDMT, and the total motor score of the UHDRS all were significant predictors of functional loss during the HD prodrome (see Table 4). There were no substantive differences between the survival analyses in which the baseline values of these risk factors were used versus models in which the risk factors were updated in a time-dependent fashion. Therefore, for simplicity, we only present findings from the fixed baseline predictors (Table 4).

DISCUSSION

Despite the need for functionally-based outcomes in clinical trials, the current findings suggest that those typically used in HD studies are not sufficient to assess functional outcomes in the 15 years showing clinical and biological changes prior to diagnosis. Over 88% of all participants in the HD prodrome scored at ceiling on the TFC and FAS at baseline. Based on these data, it is clear that future clinical trials designed to modify HD early in its biological course will require the development of new, very sensitive measures of real-life function. Since the TFC and FAS were designed to assess diagnosed patients with easily recognized motor complications, recent findings characterizing the HD prodrome and earlier phenotype of HD may require a reformulation of outcomes for clinical trials.

In those prodromal HD individuals with some early functional limitations, work and financial capacity appear to be the first areas of decline. Although only 5–7% of our sample noted a loss on these items, they were the most frequently endorsed and may serve as content areas for the development of more sensitive assessment items. Although activities of daily living (2.0%) and domestic chores (0.8%) may also be difficult during the HD prodrome, these questions are currently too vague to further develop as more sensitive items. Similarly, driving capacity (1.3%) is a complex task that may be worthwhile to evaluate, although the current items provide less direction for the development of future items. Given that the current study used the largest sample size ever tested during the HD prodrome, it is likely that the current items lack the power to be useful in future clinical trials.

Consistent with previous studies,²⁷⁻²⁹ we found that all three clinical measures of HD—motor, cognitive, and mood—were highly associated with functional capacity scores. Survival analysis indicated that no one specific measure is more or less important in predicting functional loss in early HD. Despite the traditional emphasis on the motor impairment in HD, it is interesting that our data suggest that all three domains tested were highly significant predictors of job change during the HD prodrome. To our knowledge, this is the first prospective study ever conducted on the emergence of functional loss secondary to early degeneration. The consistency of this finding across several studies suggests that functional decline in HD may be reduced by treating and limiting clinical symptom severity. In addition, these findings suggest that functional outcome measures, if measured sensitively, may be a clinically meaningful endpoint for clinical trials during the prodrome of HD (and perhaps the prodromal phases of other neurodegenerative diseases).

Although measures of depression have often been associated with impairment in HD,^{21, 27, 30-34} ours is the first known study to examine distinct components of depression in this disease. Using mood and energy factors from the BDI, it appears that fatigue, or low energy, rather than depressed affect, is more highly associated with functional impairments in the

HD prodrome. Additional research is needed to better dissect how components of “depression” vary among brain diseases and how these components may impact functionality.

Examining the rate of change on functional scales may be another method for evaluating outcomes. In manifest HD, an average rate of change of -0.72 points/year on the TFC has been reported.¹⁴ However, the rate of change may vary depending on the stage of disease. Marder and colleagues²⁸ showed rates of TFC change for manifest HD varied from -0.06 /year in earlier stage patients to -0.97 /year for later stage patients. Similarly, the current study showed that “nearness” to HD diagnosis affected TFC change rates (e.g., -0.11 points/year in the “near” group, -0.04 /year in the “mid” group, and -0.007 /year in the “far” group). Despite these variations in annual rates of TFC change, if future studies can clarify the expected rates of change, then a change in the slope of the TFC might become a useful research tool in the HD prodrome and early symptomatic populations.

Our findings suggest that the first functional impact of neurodegenerative disease may be a person's inability to maintain performance in their accustomed work. Unfortunately, most published functional scales assess independence in basic self-care items such as dressing, feeding, and ambulation. Moreover, many scales are developed for caregivers, making an implicit assumption that functioning cannot be measured until an individual relies upon others for maintenance of daily functions. Scale development for earlier functional loss may need to reflect the participants' awareness of challenges they face and what they do to compensate or overcome challenges before functional loss is apparent to others. Before demonstrating the efficacy of future treatments in normally-functioning or nearly normal-functioning individuals, subtler functional scales will need to be developed.

Despite the interesting findings, there are some noteworthy limitations to acknowledge. The two measures of functional capacity in the current study were based on self- or collateral report. Objective assessments (e.g., occupational therapy evaluations, driving evaluation) may have led to different results. Similarly, the current study used single measures of cognition, mood, and motor functioning, and other measures that tap these domains have been linked with functional abilities in different ways. Since only a fraction of individuals in the prodrome of HD are tested and participate in studies like PREDICT-HD, it is unknown how these results will generalize to the entire population. Regardless of these limitations, PREDICT-HD's goals are to identify and track functional, radiological, and clinical measures of very early HD, prior to the onset of diagnosable motor disease, to aid in the design of clinical trials of neuroprotective or disease-modifying therapies. The current results suggest specific directions to proceed in the development of sensitive functional assessment tools for this population.

**PREDICT-HD Investigators, Coordinators, Motor Raters, Cognitive Raters
(October/November 2008 data cut)**

Henry Paulson, MD, Kimberly Bastic, BA, Rachel Conybeare, BS, Clare Humphreys, Mackenzie Elbert, BS, Peg Nopoulos, MD, Robert Rodnitzky, MD, Ergun Uc, MD, BA, Leigh Beglinger, PhD, Kevin Duff, PhD, Vincent A. Magnotta, PhD, Stephen Cross, BA, Nicholas Doucette, BA, Sarah French, MA, Nancy Hale, BS, Andrew Juhl, BS, Harisa Kuburas, BA, Ania Mikos, BA, Becky Reese, BS, Beth Turner and Sara Van Der Heiden, BA (University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA);

David Ames, MD, Edmond Chiu, MD, Phyllis Chua, MD, Olga Yastrubetskaya, PhD, Phillip Dingjan, M.Psych., Kristy Draper D.Psych, Nellie Georgiou-Karistianis PhD,

Anita Goh, D.Psych, Angela Komiti, and Christel Lemmon (The University of Melbourne, Kew, Victoria, Australia);

Lynn Raymond, MD, PhD, and Joji Decolongon, MSC (University of British Columbia, Vancouver, British Columbia, Canada);

Adam Rosenblatt, MD, Christopher Ross, MD, PhD, Abhijit Agarwal, MBBS, MPH, Lisa Gourley, Barnett Shpritz, BS, MA, OD, Kristine Wajda, Claire Welsh, Arnold Bakker, MA, and Robin Miller, MS (Johns Hopkins University, Baltimore, Maryland, USA);

William M. Mallonee, MD, Greg Suter, BA, David Palmer, MD, and Judy Addison, MA (Hereditary Neurological Disease Centre, Wichita, Kansas, USA);

Ali Samii, MD, Hillary Lipe, ARNP, Thomas Bird, MD, Rebecca Logsdon, PhD, Kurt Weaver, PhD, and Katherine Field, BA (University of Washington and VA Puget Sound Health Care System, Seattle, Washington, USA);

Randi Jones, PhD, Joan Harrison, RN, Carol Ingram, RN, Cathy Wood-Siverio, MS, Stewart A. Factor, DO, J. Timothy Greenamyre, MD, PhD, and Claudia Testa MD, PhD (Emory University School of Medicine, Atlanta, Georgia, USA);

Roger A Barker, BA, MBBS, MRCP, Sarah Mason, BSC, Emma Smith, BSC, and Benjamin Wright, MBBS (Cambridge Centre for Brain Repair, Cambridge, UK);

Elizabeth McCusker, MD, Jane Griffith, RN, Bernadette Bibb, PhD, Catherine Hayes, PhD, Kylie Richardson, B LIB, and Shanthi Graham, BS (Westmead Hospital, Sydney, Australia);

Bernhard G. Landwehrmeyer, MD, Katrin Barth, Anke Niess, RN, Sonja Trautmann, Daniel Ecker, MD, Christine Held, RN, Patrick Weydt, MD, and Michael Orth, MD, PhD (University of Ulm, Ulm, Germany);

Kimberly Quaid, PhD, Melissa Wesson, MS, and Joanne Wojcieszek, MD (Indiana University School of Medicine, Indianapolis, IN);

Mark Guttman, MD, Sheryl Elliott, RN, Zelda Fonariov, MSW, Christine Giambattista, BSW, Sandra Russell, BSW, Jose Sebastian, MSW, Rustom Sethna, MD, Rosa Ip, Deanna Shaddick, Alanna Sheinberg, BA, and Janice Stober, BA, BSW (Centre for Addiction and Mental Health, University of Toronto, Markham, Ontario, Canada);

Susan Perlman, MD, Russell Carroll, Arik Johnson, MD, and George Jackson, MD, PhD (University of California, Los Angeles Medical Center, Los Angeles, California, USA);

Michael D. Geschwind, MD, PhD, Jon Gooblar, Mira Guzijan, MA, Katherine Rose, Christina Wyss-Coray, RN, Joel Kramer, PsyD, and Sharon Sha and Margaret Wetzell, BS (University of California San Francisco, California, USA);

Tom Warner, MD, PhD, Stefan Kloppel, MD, Maggie Burrows, RN, BA, Thomasin Andrews, MD, BSC, MRCP, Elisabeth Rosser, MBBS, FRCP, Sarah Tabrizi, BSC, PhD, and Charlotte Golding, PhD (National Hospital for Neurology and Neurosurgery, London, UK);

Anne Rosser, MD, PhD, MRCP, Jenny Naji, PhD, BSC, Kathy Price, RN, and Olivia Jane Handley, PhD, BS (Cardiff University, Cardiff, Wales, UK);

Peter Como, PhD, Amy Chesire, Charlyne Hickey, RN, MS, Carol Zimmerman, RN, Timothy Counihan, MD, Frederick Marshall, MD, Christina Burton, LPN, and Mary Wodarski, BA (University of Rochester, Rochester, New York, USA);

Oksana Suchowersky, MD, FRCPC, Sarah Furtado, MD, PhD, FRCPC, Mary Lou Klimek, RN, BN, MA, and Dolen Kirstein, BSC (University of Calgary, Calgary, Alberta, Canada);

Diana Rosas, MD, MS, Melissa Bennett, Jay Frishman, CCRP, Yoshio Kaneko, BA, Talia Landau, BA, Martha Lausier, CNRN, Lindsay Muir, Lauren Murphy, BA, Anne Young, MD, PhD, Colleen Skeuse, BA, Natlie Balkema, BS, Wouter Hoogenboom, MSC, Catherine Leveroni, PhD, Janet Sherman, PhD, and Alexandra Zaleta (Massachusetts General Hospital, Boston, Massachusetts, USA);

Peter Panegyres, MB, BS, PhD, Carmela Connor, BP, MP, DP, Elizabeth Vuletich, BSC, Mark Woodman BSC, and Rachel Zombor (Neurosciences Unit, Graylands, Selby-Lemnos & Special Care Health Services, Perth, Australia);

Joel Perlmutter, MD, Stacey Barton, MSW, LCSW, and Melinda Kavanaugh, MSW, LCSW (Washington University, St. Louis, Missouri, USA);

Sheila A Simpson, MD, Gwen Keenan, MA, Alexandra Ure, BSC, and Fiona Summers, DClinPsychol (Clinical Genetics Centre, Aberdeen, Scotland, UK);

David Craufurd, MD, Ruth Fullam, BSC, Rhona Macleod, RN, PhD, Andrea Sollom, MA, and Elizabeth Howard, MD (University of Manchester, Manchester, UK)

Pietro Mazzoni, MD, PhD, Karen Marder, MD, MPH, Jennifer Williamson, MS, Carol Moskowitz, MS, RNC, and Paula Wasserman, MA (Columbia University Medical Center, New York, New York, USA);

Lauren Seeberger, MD, Alan Diamond, DO, Diane Erickson, RN, Deborah Judd, RN, Terri Lee Kasunic, RN, Lisa Mellick, Dawn Miracle, BS, MS, Carol Greenwald, MD, Kristi Malleck, BS, Sherrie Montellano, MA, Rajeev Kumar, MD, and Jay Schneiders, PhD (Colorado Neurological Institute, Englewood, Colorado, USA);

Vicki Wheelock, MD, Terry Tempkin, RNC, MSN, Joseph Marsano, and Kathleen Baynes, PhD (University of California Davis, Sacramento, California, USA);

Joseph Jankovic, MD, Christine Hunter, RN, CCRC, William Ondo, MD, and Carrie Martin, LMSW-ACP (Baylor College of Medicine, Houston, Texas, USA);

Justo Garcia de Yebenes, MD, Monica Bascunana Garde, Marta Fatas, Christine Schwartz, Dr. José Lopez Sendon, MD, and Patricia Marquez Trigo (Hospital Ramón y Cajal, Madrid, Spain);

Martha Nance, MD, Dawn Radtke, RN, Deanna Norberg, BA, and David Tupper, PhD (Hennepin County Medical Center, Minneapolis, Minnesota, USA);

Wayne Martin, MD, Pamela King, BScN, RN, Marguerite Wieler, MSc, PT, Sheri Foster, and Satwinder Sran, BSC (University of Alberta, Edmonton, Alberta, Canada);

Richard Dubinsky, MD, Carolyn Gray, RN, CCRC, and Phillis Switzer (University of Kansas Medical Center, Kansas City, Kansas, USA).

Steering Committee

Jane Paulsen, PhD, Principal Investigator, Douglas Langbehn, MD, PhD, and Hans Johnson, PhD (University of Iowa Hospitals and Clinics, Iowa City, IA); Elizabeth Aylward, PhD (University of Washington and VA Puget Sound Health Care System, Seattle, WA); Kevin Biglan, MD, Karl Kiebertz, MD, David Oakes, PhD, Ira Shoulson, MD (University of Rochester, Rochester, NY); Mark Guttman, MD (The Centre for Addiction and Mental Health, University of Toronto, Markham, ON, Canada); Michael Hayden, MD, PhD (University of British Columbia, Vancouver, BC, Canada); Bernhard

G. Landwehrmeyer, MD (University of Ulm, Ulm, Germany); Martha Nance, MD (Hennepin County Medical Center, Minneapolis, MN); Christopher Ross, MD, PhD (Johns Hopkins University, Baltimore MD); Julie Stout, PhD (Indiana University, Bloomington, IN, USA and Monash University, Victoria, Australia).

Study Coordination Center

Steve Blanchard, MSHA, Christine Anderson, BA, Ann Dudler, Machel Henneberry, Kelsey Montross, BA, Philip O'Brien, MA, Elizabeth Penziner, MA, Anne Leserman, MSW, LISW, Bryan Ludwig, BA, Brenda McAreavy, James A. Mills, MS, Gerald Murray, PhD, Carissa Nehl, BS, Stacie Vik, BA, Chiachi Wang, MS, and Christine Werling-Witkoske (University of Iowa).

Clinical Trials Coordination Center

Keith Bourgeois, BS, Catherine Covert, MA, Susan Daigneault, Elaine Julian-Baros, BS, CCRC, Kay Meyers, BS, Karen Rothenburgh, Beverly Olsen, BA, Constance Orme, BA, Tori Ross, MA, Megan Simone, MOL, Joseph Weber, BS, and Hongwei Zhao, PhD (University of Rochester, Rochester, NY).

Cognitive Coordination Center

Julie C. Stout, PhD, Sarah Queller, PhD, Shannon A. Johnson, PhD, J. Colin Campbell, BS, Eric Peters, BS, Noelle E. Carlozzi, PhD, and Terren Green, BA, Shelley N. Swain, MA, David Caughlin, BS, Bethany Ward-Bluhm, BS, Kathryn Whitlock, MS (Indiana University, Bloomington, Indiana, USA; Monash University, Victoria, Australia; and Dalhousie University, Halifax, Canada).

Recruitment and Retention Committee

Jane Paulsen, PhD, Elizabeth Penziner, MA, Stacie Vik, BA (University of Iowa, USA); Abhijit Agarwal, MBBS, MPH, Amanda Barnes, BS (Johns Hopkins University, USA); Greg Suter, BA (Hereditary Neurological Disease Center, USA); Randi Jones, PhD (Emory University, USA); Jane Griffith, RN (Westmead Hospital, AU); Hillary Lipe, ARNP (University of Washington, USA); Katrin Barth (University of Ulm, GE); Michelle Fox, MS (University of California, Los Angeles, USA); Mira Guzjian, MA, Andrea Zanko, MS (University of California San Francisco, USA); Jenny Naji, PhD (Cardiff University, UK); Rachel Zombor, MSW (Graylands, Selby-Lemnos & Special Care Health Services, AU); Melinda Kavanaugh (Washington University, USA); Amy Chesire, Elaine Julian-Baros, BS, CCRC, Elise Kayson, MS, RNC (University of Rochester, USA); Terry Tempkin, RNC, MSN (University of California Davis, USA); Martha Nance, MD (Hennepin County Medical Center, USA); Kimberly Quaid, PhD (Indiana University, USA); and Julie Stout, PhD (Indiana University, Bloomington, IN, USA and Monash University, Victoria, Australia).

Event Monitoring Committee

Jane Paulsen, PhD, William Coryell, MD (University of Iowa, USA); Christopher Ross, MD, PhD (Johns Hopkins University, Baltimore MD); Elise Kayson, MS, RNC, Aileen Shinaman, JD (University of Rochester, USA); Terry Tempkin, RNC, ANP (University of California Davis, USA); Martha Nance, MD (Hennepin County Medical Center, USA); Kimberly Quaid, PhD (Indiana University, USA); Julie Stout, PhD (Indiana University, Bloomington, IN, USA and Monash University, Victoria, Australia); and Cheryl Erwin, JD, PhD (McGovern Center for Health, Humanities and the Human Spirit, USA).

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Authors' Roles:

1. Research project: A. Conception, B. Organization, C. Execution, D. Review and Critique;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript: A. Writing of the first draft and all revisions, B. Review and Critique;

Paulsen: 1A, 1B, 1C, 1D, 2A, 2C, 3A, 3B. **Wang:** 2B, 2C, 3A, 3B. **Duff:** 1B, 1C, 2C, 3B. **Barker:** 1C, 2C, 3B. **Nance:** 1A, 1C, 2C, 3B. **Beglinger:** 1A, 2C, 3B. **Moser:** 2C, 3B. **Williams:** 1A, 2C, 3B. **Simpson:** 1C, 3B. **Langbehn:** 1A, 1C, 2A, 2B, 2C, 3B. **van Kammen:** 1D, 2C, 3B.

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TABLE 1

Percent and number of prodromal HD participants not endorsing maximum scores on items from the FAS and TFC

FAS Item	Percent	N
Could participant engage in gainful employment in his/her accustomed work?	7.7	60 ^a
Could participant engage in any kind of gainful employment?	2.8	22 ^a
Could participant manage his/her finances (monthly) without any help?	2.2	17 ^a
Could participant operate an automobile safely and independently?	1.3	10 ^a
Could participant engage in any kind of volunteer or non-gainful work?	1.0	8 ^a
Could participant shop for groceries without help?	0.5	4 ^a
Could participant use public transportation to get places without help?	0.5	4 ^a
TFC Item		
OCCUPATION: 3 = normal		
2 = reduced capacity for usual job	5.5	43 ^b
1,0 = marginal work and unable	2.7	21 ^b
FINANCES: 3 = normal		
2 = slight assistance	2.8	22 ^b
1,0 = major assistance and unable	0.5	4 ^b
ADL: 3 = normal		
2,1,0 = minimal impairment and total care	2.0	16 ^b
DOMESTIC CHORES: 2 = normal		
1,0 = impaired and unable	0.8	6 ^b

^a n = 784;

^b n = 783;

FAS = Functional Assessment Scale; TFC = Total Functional Capacity; ADL = Activities of Daily Living

TABLE 2

Logistic regression for engagement in accustomed work

	Odds Ratio/unit (OR)	Log OR	S.E. of Log OR	Chi-Square	p-value
SDMT	1.054	0.053	0.016	11.47	0.0007
BDI Energy	0.723	-0.324	0.068	22.58	<0.0001
BDI Mood	0.957	-0.044	0.033	1.75	0.18
Motor Total	0.915	-0.089	0.024	13.24	0.0003

n = 775; BDI = Beck Depression Inventory; SDMT = Symbol Digit Modality Test Results are from a multivariate model with the above four predictors tested simultaneously.

TABLE 3

Rates of change on clinical outcome measures in prodromal HD

	Near Diagnosis		Mid Diagnosis		Far Diagnosis	
	Mean (SD)	p-value	Mean (SD)	p-value	Mean (SD)	p-value
FAS	-0.143 (0.02)	<0.0001	-0.06 (0.02)	0.004	-0.02 (0.018)	0.26
TFC	-0.142 (0.02)	<0.0001	-0.046 (0.02)	0.02	-0.017 (0.02)	0.37
BDI	0.30 (0.17)	0.08	-0.47 (0.16)	0.002	-0.09 (0.15)	0.53
BDI Mood	0.01 (0.09)	0.95	-0.17 (0.08)	0.03	-0.10 (0.08)	0.20
BDI Energy	0.10 (0.05)	0.04	-0.15 (0.04)	0.002	0.00 (0.04)	0.96
SDMT	-0.77 (0.18)	<0.0001	0.15 (0.16)	0.35	0.75 (0.16)	<0.0001
Motor Total	1.69 (0.14)	<0.0001	0.64 (0.13)	<0.0001	0.27 (0.12)	0.03

FAS = Functional Assessment Scale; TFC = Total Functional Capacity; BDI = Beck Depression Inventory; SDMT = Symbol Digit Modality Test

TABLE 4

Survival analysis for loss of accustomed work with baseline predictors

	Log Hazard Ratio/Unit	S.E.	Chi Square	p-value	Hazard Ratio/Unit
SDMT	-0.045	0.011	16.28	<0.0001	0.956
BDI energy	0.244	0.055	19.47	<0.0001	1.276
BDI mood	-0.032	0.03111	1.08	0.29	0.969
Motor Total	0.065	.0160	16.63	<0.0001	1.067

N = 643 with all data; BDI = Beck Depression Inventory; SDMT = Symbol Digit Modality Test. Results are from a multivariate model with the above four predictors tested simultaneously.