PROGRAM
Inaugural
Huntington Disease
Clinical Research Symposium
Organized by the Huntington Study Group

To be held on Saturday, 1 December 2007, in the Rooftop Ballroom at the Omni Parker House, Boston, Massachusetts, USA.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The University of Rochester School of Medicine and Dentistry designates this educational activity for a maximum of 4.75 credits in the AMA PRA Category 1 Credit™ system. Physicians should claim credit only commensurate with the extent of their participation in the activity.

The Symposium consists of three keynote addresses and four platform presentations by the following individuals, with allotted time for questions and answers after each presentation.

7:30–9:00 AM

Poster viewing.

9:05–9:45 AM

KEYNOTE ADDRESS—HD Unmet Clinical Research Needs: Perspective From the Pre-Manifest HD Population.

Katharine Moser, OTR/L. Terence Cardinal Cooke Health Care Center, New York, NY, USA.

9:45–10:00 AM

PLATFORM PRESENTATION—Subtle Motor Abnormalities in Pre-Manifest HD Are Associated With Gene Status, Probability of Disease Onset, and Striatal Atrophy.

K.M. Biglan,¹ C.A. Ross,² D.R. Langbehn,³ E. Aylward,⁴ J.C. Stout,⁵ S. Queller,³ N. Carlozzi,³ K. Duff,³ L.J. Beglinger,³ J.S. Paulsen,³ and the PREDICT-HD Investigators of the Huntington Study Group. ¹University of Rochester Medical Center, USA, ²Johns Hopkins University, USA, ³University of Iowa, USA, ⁴Washington University, USA, and ⁵University of Indiana, USA.

Background: The PREDICT-HD study seeks to identify refined clinical and biological markers of disease onset in pre-manifest individuals, at risk for HD, who have undergone predictive genetic testing. We present the baseline assessment of motor evaluations and their relationship to predicted onset and striatal volumes.

Methods: We compared baseline motor data from the UHDRS between gene carriers (cases) and non-gene carriers (controls) using *t*-tests and chi-square. Predicted probability of onset was calculated per Langbehn et al. [Clin Genet 2004;65:267–277; erratum in: Clin Genet 2004;66:81]. Gene carriers were categorized as near, mid, or far from onset based on the predicted

onset. Striatal volumes were calculated using MRI measurements per Aylward et al. [Mov Disord 2000;15:552–560]. Multiple linear regression associating total motor score, motor domains, and individual motor items with predicted onset and striatal volumes were performed, adjusting for age and gender. Analysis for trends of baseline demographic and motor items for the near, mid, and far from onset groups were conducted.

Results: Gene carriers were older and had worse total motor scores and greater striatal atrophy than non-gene carriers ($P \leq 0.0001$). Higher total motor scores at baseline were associated with higher probability of disease onset (partial $R^2 = 0.14$, $P < 0.0001$) and greater striatal atrophy (partial $R^2 = 0.07$, $P < 0.0001$). These findings were most notable for oculomotor, bradykinesia, and chorea domains of the UHDRS. A trend for increasing scores with increasing proximity to onset (near, mid, far) was seen for total motor and all motor domains except rigidity ($P < 0.01$ for all).

Conclusions: The motor UHDRS is sensitive to subtle motor abnormalities in pre-manifest HD and aids in distinguishing gene carriers from non-gene carriers. Even in this pre-manifest population, small differences in UHDRS motor items were associated with a higher probability of disease onset and greater striatal atrophy on imaging, but only a small proportion of the variance associated with these outcomes. Longitudinal assessment will be critical in determining whether baseline UHDRS motor items are sensitive predictors of actual disease onset and progression of striatal atrophy.

10:00–10:15 AM

PLATFORM PRESENTATION—Optimal Measurement of Clinical and Biological Markers for Clinical Trials: The HD Toolkit Project.

J.C. Stout,^{1,2} A. Tomusk,² S. Queller,² S. Lifer,² S. Hastings,² J. Dawson,² B. Walker,² K. Whitlock,² and S. Johnson.³ ¹Monash University, Australia, ²Indiana University, USA, and ³Dalhousie University, Canada.

Aims: Search is underway for neuroprotective compounds that can prevent HD or slow its progression. Studies such as PREDICT-HD, PHAROS, COHORT, and Registry are investigating critical methodology necessary for identification of participants and sensitive measurement tools in preparation for neuroprotective clinical trials. The HD Toolkit project is a vital ongoing effort, funded by the High Q Foundation, to extend these efforts by examining the published and unpublished literature to identify clinical and biological markers that show measurable deterioration over relatively short intervals (1–2 years), synthesize ongoing findings, and facilitate evidence-based approaches to the

selection of optimum clinical and biological markers without which neuroprotective drug effects cannot be detected.

Methods: The HD Toolkit project utilizes the principles of evidence-based medicine to guide systematic review and meta-analysis of measurement tools extracted from published articles (>10,000) and unpublished sources. Findings from the meta-analysis are integrated with advice from expert consultants and pragmatic issues to make recommendations for measurement selection in studies of pre-diagnostic and early HD.

Results: Meta-analysis of more than 300 clinical markers has yielded several tests with clear evidence of sensitivity or insensitivity in pre-diagnostic and early HD. Cognitive and psychomotor tests with demonstrated sensitivity include Trails-B, Stroop Word, University of Pennsylvania Smell Identification Test, and speeded finger tapping. Tests with demonstrated longitudinal insensitivity in pre-diagnostic HD include Stroop Interference and Letter Fluency. A secondary function of the HD Toolkit is to identify promising measures that have yet to be adequately vetted in pre-diagnostic and early HD, and to promote investigation of these measures. Promising measures include gait analysis, kinematic drawing analysis, and visual perspective-taking tasks.

Conclusions: In preparation for clinical trials, the HD Toolkit project offers no-cost consultation (website under development) providing an evidence-based resource for selecting and analyzing outcome measures with detectable sensitivity to early disease progression in HD.

10:15–11:00 AM

Break and poster viewing.

11:00–11:40 AM

KEYNOTE ADDRESS—Emerging Clinical Candidates From the CHDI Pipeline.

Robert Pacifici, PhD. *CHDI, Inc., Los Angeles, CA, USA.*

11:40–11:55 AM

PLATFORM PRESENTATION—PHEND-HD: A Safety, Tolerability, and Biomarker Study of Phenylbutyrate in Symptomatic HD.

S. Hersch for the Huntington Study Group PHEND Investigators. *Massachusetts General Hospital, USA.*

Background: Studies in cellular models and in invertebrate and transgenic mouse models of Huntington's disease have consistently suggested that histone deacetylase (HDAC) inhibition may be therapeutic in human HD. In these models, HDAC inhibitors reduce histone acetylation, slow physiological or functional decline, ameliorate neurodegeneration, and prolong survival. While a variety of broad and selective HDAC inhibitors are in development, phenylbutyrate has been used for many years for a variety of disorders, and there is substantial clinical experience with it. A small study recently suggested the maximally tolerated dose of phenylbutyrate in HD to be about 15 grams daily.

Aims: To evaluate the safety, tolerability, clinical impact, and biological impact of phenylbutyrate in early symptomatic HD.

Methods: A multicenter safety and tolerability study of 15 grams daily phenylbutyrate was performed in 60 early symptomatic subjects with HD, in collaboration with the HSG. After an initial one-month long, randomized, placebo-controlled exposure, subjects received open-label treatment for 12 additional weeks. Assessments included clinical measures of tolerability, the UHDRS, standard safety laboratory studies, and a blinding assessment. Supplementary biological measures included fetal

hemoglobin, plasma glutamine, histone acetylation and gene expression in lymphocytes, plasma levels of phenylbutyrate and metabolites, and metabolomic profiling.

Results: Phenylbutyrate was safe and well tolerated in early symptomatic HD subjects taking 15 grams daily. In the double-blind phase, neither subjects nor investigators correctly predicted whether the compound was active or a placebo. Levels of phenylbutyrate and metabolites were measurable in blood as well as leukocyte histone acetylation, a pharmacodynamic biomarker of HDAC inhibition that responded to treatment.

Conclusions: Fifteen grams daily of phenylbutyrate is safe and well tolerated and results in PK/PD responses supportive of further clinical development. Our data illuminate possible biomarkers for this and other HDAC inhibitors.

11:55–12:10 PM

PLATFORM PRESENTATION—A Randomized, Controlled Trial of Ethyl-EPA for the Treatment of Huntington Disease: 12-Month Results.

E.R. Dorsey for the Huntington Study Group TREND-HD Investigators. *University of Rochester Medical Center, USA.*

Background: Ethyl-eicosapentaenoic acid (ethyl-EPA), an omega-3 fatty acid, was not an effective treatment for Huntington disease at 2 grams daily in the primary 6-month double-blind study. Participants who completed the double-blind phase were given the opportunity to take open-label ethyl-EPA 2 grams daily for the following 6 months.

Aim: To assess the efficacy of ethyl-EPA over 12 months.

Methods: We conducted a multicenter, randomized, double-blind, placebo-controlled trial in North America of ethyl-EPA (1 gram twice daily) for 6 months followed by a 6-month open-label study. The prespecified primary outcome measure was the change in the Total Motor Score 4 (TMS-4) component of the Unified Huntington's Disease Rating Scale. We restricted analysis of the 12-month results to those study participants who completed the open-label phase before April 24, 2007, when results of the primary analysis indicating no therapeutic benefit of ethyl-EPA in the study's 6-month double-blind portion were released.

Results: Of the 316 individuals enrolled in the 12-month study, 190 completed the open-label study before April 24, 2007. Their baseline features were generally similar to the whole study population. At 12 months, the TMS-4 change for those who were originally randomized to ethyl-EPA was significantly better than for those who were originally randomized to placebo (0.0 point change versus 1.8 point worsening; $P = 0.02$), especially for those with a CAG repeat less than 45 (1.2 point improvement versus 1.6 point worsening; $P = 0.004$). Differences favoring 12 months of continuous ethyl-EPA were also found on chorea but not on measures of global improvement, function, or cognition.

Conclusions: Motor features of participants receiving ethyl-EPA for 12-months were improved compared with those receiving placebo for 6 months followed by ethyl-EPA for 6 months. In view of the negative results at 6 months, these findings require confirmation in longer term, controlled studies of ethyl-EPA.

12:10–12:50 PM

KEYNOTE ADDRESS—Experimental Therapeutics for Huntington's Disease: Challenges and Hurdles to Successful Clinical Development.

Russell Katz, MD. *U.S. Food and Drug Administration, USA.*

POSTER SESSION

Posters will be staffed from 7:30–9:00 AM and 10:15–11:00 AM in the Rooftop Ballroom.

CLINICAL STUDIES

POSTER 1

Abstract withdrawn.

POSTER 2

First Report of Huntington's Disease in West Asian Immigrants Living in the United States.

T. Tempkin and V. Wheelock. *UC Davis School of Medicine, USA.*

Objective: To describe the clinical features of Huntington's disease in two West Asian immigrant families in Northern California.

Background: Huntington's disease (HD) prevalence differs significantly among ethnic populations. Europeans have the highest prevalence rates; lower rates have been reported in Japan, in China, and in people of African origin. HD in India was first reported in 1955, and was subsequently reported in West Asian immigrants in the United Kingdom in 1981. A subsequent report describing 26 HD patients from India found that 15% of cases had juvenile onset. There are no previous reports of HD cases originating in West Asian (Indian) patients residing in the USA.

Methods: Case report.

Results: Among 197 HD patients followed at our center, we identified 3 patients from two families who emigrated from India. Two patients (siblings) had juvenile-onset HD, both with maternal inheritance, and one had mid-life onset. In family A, there was a history of progressive chorea and dementia with death at age 35 in the mother of three siblings. The oldest sibling developed progressive cognitive decline and chorea starting at age 14, with clinical diagnosis made at age 19. The second asymptomatic sibling tested negative for the HD gene at age 30, and the third sibling developed subtle motor symptoms at age 19, followed by cognitive difficulties at age 20, with CAGn of 62. In family B, a 44-year-old man presented to the clinic with a history of chorea and progressive memory problems starting at age 35. He had a family history of a similar disorder in his mother. Diagnosis was confirmed with genetic testing showing CAGn of 45.

Conclusions: The diagnosis of HD should be considered in West Asian patients presenting with chorea and cognitive and psychiatric symptoms, particularly if there is a positive family history. Juvenile HD may be more common in this population.

POSTER 3

SCA2 Mimicking Juvenile Onset HD: A Case Report.

G. Schwartz,¹ J. Corey-Bloom,^{2,3} P. Mattis,¹ and A. Feigin.¹
¹North Shore University Hospital, USA, ²UC San Diego, USA, and ³VA San Diego Healthcare System, USA.

Objective: To report a case of SCA2 mimicking juvenile HD.

Background: SCA2 has been reported to present with a widely varying clinical phenotype. Some descriptions in the literature

include juvenile-onset parkinsonism, dystonia, chorea, and impaired oculomotor function.

Methods: Case report.

Results: A 13-year-old girl, with a reported family history of HD, presented for evaluation at our HD clinic. The patient's mother was reported to have HD beginning at age 20 during her first pregnancy; she was placed in a nursing home in her early 30s and died at age 42. Other affected family members include one of two siblings, a maternal aunt, grandmother, great-uncle, great-grandmother, and great-great-grandfather. The patient was doing well in eighth grade. One year prior she had undergone an elective 2nd trimester abortion following an unplanned pregnancy. During her pregnancy it was noted that she began slurring her words and had episodes of poor coordination, occasionally resulting in falls. Neurological examination revealed mildly impaired rapid alternating movements, impaired Luria, and dysarthria. Over the subsequent 8 years, there was a gradual progression of her symptoms, with severely slowed ocular saccades, worsening dysarthria, parkinsonism, mild generalized chorea, dystonia, postural instability, and behavioral changes marked by anger, irritability, and social withdrawal. Neuropsychological testing at age 18 revealed average general cognitive functioning, with significant difficulties in the domains of attention and executive functioning. Recent follow-up by phone revealed that the patient's affected brother tested positive for SCA2, and HD genetic testing in the patient was negative (15 and 18 CAG repeats).

Conclusions: The SCA2 mutation can produce a clinical phenotype that mimics juvenile HD. The case presented here was notable for the lack of cerebellar findings such as ataxia. In patients presenting with a juvenile HD phenotype, SCA2 should be considered in the differential diagnosis.

POSTER 4

Long-Term Treatment with Olanzapine and Risperidone in Relation to Dystonia in Huntington's Disease.

P. Young,¹ D.L. McArthur,² and S. Perlman.¹ ¹UCLA Medical Center, USA, and ²David Geffen School of Medicine at UCLA, USA.

Objective: To evaluate occurrence and degree of dystonia in relation to long-term treatment with olanzapine and risperidone, for the control of motor and psychiatric symptoms of Huntington's disease.

Background: Dystonia in adult-onset HD increases as the disease progresses. Olanzapine and risperidone have been found to induce both focal and generalized dystonias. Atypical neuroleptics may induce early onset dystonia, which may accelerate functional decline.

Methods and Results: A retrospective analysis of medical records from 64 Huntington's disease patients was performed. Patients included those treated with olanzapine ($n = 23$, average age 53.3 years), risperidone ($n = 18$, average age 46.2 years), or nothing ($n = 23$, average age 51.4 years). All but 4 patients had genetically confirmed HD, with an average CAG repeat length of 44.4 for all patients.

Dystonia was assessed by reviewing Unified Huntington's Disease Rating Scale records and written reports from two examiners. Occurrence and severity of dystonia were deter-

mined in five body regions with a 0–4 rating as set forth in the UHDRS. Total dystonia was the sum of scores observed in each body region (range 0–20). Average disease duration was 8.1, 11.5, and 10.1 years for control, olanzapine, and risperidone groups, respectively. There was a modest positive correlation ($r = 0.22$) between disease duration and average dystonia score across all patients.

Mean dose of olanzapine and risperidone were 8.9 mg/day (range 2.5–30 mg/day) and 2.4 mg/day (range 0.5–5 mg/day), respectively, over an average treatment duration of 2.9 years for all groups (range 0–8 years). Dystonia scores averaged 2.1, 4.0, and 2.8 for the control, olanzapine-treated, and risperidone-treated groups, respectively, over the treatment period, but no significant differences were found in dystonia scores between groups using mixed effects modeling.

Conclusions: Use of olanzapine and risperidone at common dosages to treat motor and psychiatric symptoms of Huntington's disease does not significantly alter occurrence or severity of dystonia.

POSTER 5

Long-Term Effects of Olanzapine on Motor Features and Weight in Huntington's Disease.

V. Wheelock,¹ T. Tempkin,¹ S. Perlman,² C. Higginson,³ L. Carr,⁴ and K. Sigvardt.^{1,5,6} ¹UC Davis Medical Center, USA, ²UCLA Medical Center, USA, ³Loyola College in Maryland, USA, ⁴Michigan State University, USA, ⁵UC Davis, USA, and ⁶VA Northern California Health Care System, USA.

Objective: We describe the long-term effects of olanzapine on motor features and weight in a cohort of patients with Huntington's disease (HD).

Background: Olanzapine is an atypical neuroleptic with high selective affinity for dopamine D₂ and serotonin 5HT₂ receptors, suggesting possible efficacy as an anti-chorea agent. Previous small, open-label trials of olanzapine in HD have shown efficacy for chorea over the short term.

Methods: This is a retrospective analysis of the effects of olanzapine prescribed in open-label fashion to HD patients at two HDSCA Centers of Excellence. Indications for olanzapine included chorea, frequent aggressive outbursts, or both. Subjects were excluded if taking other neuroleptic medications or if pre- and post-treatment treatment UHDRS scores were not available. Olanzapine was started at 1.25–5 mg/day and gradually titrated to the dose judged to be clinically effective. Baseline and last observation UHDRS motor scores (total motor, chorea and bradykinesia subscore) and weight were analyzed using a mixed factor ANOVA with clinical site as the between-subjects variable and baseline/after treatment as the within-subjects variable. Alpha was set to 0.05.

Results: There were 41 patients (17 male). Mean age was 50 years, duration of HD was 9.4 years; TFC was 6, and (CAG)n was 45. The clinical indication for treatment with olanzapine was chorea in 27, behavioral problems in 8, or both in 6. The average dose was 10.4 mg/day (range 1.25–30 mg). The average duration of treatment was 20.9 months (range 3–59 months). Baseline chorea score was 9.4 ± 4.9 , and last observation chorea score was 6.8 ± 5 , a 27.5% reduction ($P < 0.01$). Mean weight gain was 3.9 kg ($P < 0.05$). No patient developed clinically significant bradykinesia or akathisia. There were no deaths or cardiovascular or cerebrovascular events. Seven patients stopped treatment: three for lack of efficacy, one for agitation, and three for weight gain.

Conclusions: Olanzapine treatment produced a sustained anti-chorea effect and mild weight gain in this cohort. Olanzapine should be considered for treatment of disabling chorea, partic-

ularly in patients with weight loss. A prospective randomized trial of olanzapine for treatment of chorea is warranted.

POSTER 6

COHORT: A Snapshot of Baseline Characteristics.

M.C. Chiriac, A. Shinaman, I. Shoulson, and the Huntington Study Group CoHort Investigators. *University of Rochester Medical Center, Clinical Trials Coordination Center, USA.*

Background: COHORT is a prospective observational study involving research participants who are 1) manifest Huntington's disease (HD), 2) pre-manifest HD (100% risk) by virtue of DNA testing, and 3) at risk for HD (nominally 50% risk) unaware of gene status, as well as 4) family members without risk for HD. The major objectives of COHORT are to accrue systematic clinical assessments (e.g., UHDRS), collect and store selected biological samples (e.g., DNA), make available de-identified clinical/hereditary data and biological material for scientific research (COHORT/Coriell website <http://ccr.coriell.org>), and help expedite recruitment of subjects for future therapeutic trials.

Methods: We analyzed baseline demographic and clinical data for the four groups of participants who had enrolled in COHORT as of June 24, 2007. The 654 participants comprised four groups: 1) manifest: $n = 356$ (54%), age 52 ± 11.6 years, 52% female; 2) pre-manifest: $n = 58$ (9%), 40 ± 11.9 years, 72% female; 3) at risk: $n = 98$ (15%), 44 ± 15.1 years, 71% female; and 4) no risk: $n = 142$ (22%), 53 ± 11.9 years, 52% female.

Results: Individuals without risk for HD were more likely to be married and employed and without history of depression than clinically unaffected participants who were at risk or known to carry the HD gene.

Conclusions: In contrast to individuals with manifest or no risk of HD, there is a female predominance of research participation among individuals at high risk for HD in COHORT and other observational studies (PHAROS, PREDICT-HD). Although COHORT participants without risk of HD share many burdens and stress with their family members who are at high risk for HD, they are more likely to be married, gainfully employed, and report less depression.

POSTER 7

Predictive Value of CAG Repeat Length for HD Onset: Effects of Ethnicity, Demographic, and Clinical Variables.

A.E. Kane,¹ G.M. Peavy,¹ J.L. Goldstein,¹ M.W. Jacobson,^{1,2} S. Lessig,^{1,2} L. Wasserman,¹ and J. Corey-Bloom.^{1,2} ¹UC San Diego, USA, and ²VA San Diego Healthcare System, USA.

Objective: To examine demographic and clinical factors associated with variability in age of onset in a heterogeneous sample of individuals with Huntington's disease (HD).

Background: The importance of CAG repeat length in determining age of onset in HD has been well documented; however, considerable variability in phenotypic expression remains after controlling for repeat length, especially at the lower end of the repeat spectrum (i.e., 39–43). Investigating CAG repeat length in an ethnically diverse sample could improve our prediction of HD onset, especially when combined with clinical and demographic information.

Methods: 184 affected individuals, including 31 Hispanics, followed prospectively, were genotyped for CAG repeat length ($M = 45.6$). Gender, ethnicity, education, affected parent, depression, and substance abuse were also examined as predictors of age of onset ($M = 41.9$), using hierarchical multiple regres-

sion. Potential ethnic differences were examined using one-way ANOVA.

Results: In the entire cohort, CAG repeat length accounted for 54% of the variance in age of onset ($P < 0.001$), with the remaining factors each uniquely accounting for $<1\%$ of the variance. In individuals with CAG repeat length of <44 ($n = 77$), however, CAG repeat length accounted for only 21% of the variance, with demographic and clinical variables accounting for an additional 12%. Despite comparable mean CAG repeat length and age of onset, the relationship between these two variables was much stronger in the Hispanic than in the Caucasian group ($R^2 = 0.61$ vs 0.53). Dramatic ethnic differences emerged for individuals with repeat lengths of <44 : CAG repeat length accounted for only 17% of the variance in age of onset for Caucasians, compared with 86% for Hispanics.

Conclusions: The extreme variability in age of onset at the low end of the CAG repeat spectrum demonstrates the importance of identifying potential modifying factors and including an ethnically diverse sample in predictive models of HD.

POSTER 8

Five Years of Monitoring the Safety and Feasibility of PHAROS (Prospective Huntington At Risk Observational Study).

E.P. Kayson and the Huntington Study Group PHAROS Investigators. *University of Rochester Medical Center, USA.*

Objective: PHAROS [Arch Neurol 2006;63:991–996] aims to identify factors that affect the feasibility and safety of long-term trials in unaffected individuals who may carry the Huntington's disease (HD) gene.

Methods: Protocol adherence, mental health, life events, and retention of participants were monitored from the first PHAROS enrollment in July 1999 and were analyzed without knowledge of HD (CAGn) gene status.

Results: 1001 PHAROS participants, aged 41.3 ± 7.3 years, were enrolled at 43 Huntington Study Group (HSG) research sites and were re-evaluated at ~ 9 -month intervals over an average of 5 years of follow-up. As of May 2007, a total of 811 reported events of pre-specified interest involved 546 participants, including a 3.9% annual incidence of heightened suicide risk (five suicide attempts but no resulting deaths) and a 2.5% annual incidence of medical hospitalizations. In all, 215 subjects withdrew consent to participate; 48 (4.8%) withdrawals occurred in the initial year of the study. Withdrawal rates for the second, third, fourth, and fifth visits were 4.7%, 4.6%, 3.3%, and 4.5%, respectively. Of the 786 participants actively followed, 72% were seen within the past 12 months.

Conclusions: Longitudinal research involving unaffected individuals at risk for HD appears to be safe and feasible over a 5-year period of observation. The average annual withdrawal rate in PHAROS stayed approximately constant over more than 5 years of follow-up. The design of long-term trials needs to consider the ongoing mental health of research participants and the pace of consent withdrawal, which might expectedly be less in interventional than in observational studies.

CLINICAL/BIOMARKER STUDIES

POSTER 9

Brain Correlates of Neuropsychological Function in Pre-symptomatic HD Gene Carriers.

P. Mattis,^{1,2} C. Tang,^{1,2} D. Zgaljardic,³ Y. Ma,^{1,2} V. Dhawan,^{1,2} M. Guttman,⁴ J.S. Paulsen,⁵ D. Eidelberg,^{1,2} and A. Feigin.^{1,2} ¹Feinstein Institute for Medical Research, North Shore-LIJ Health System, USA, ²North Shore University Hos-

pital and New York University School of Medicine, USA, ³Transitional Learning Center, USA, ⁴University of Toronto, Canada, and ⁵University of Iowa, USA.

Objective: To identify regional brain metabolic correlates of neuropsychological function in presymptomatic HD gene carriers (pHD).

Background: Subtle cognitive and behavioral symptoms may emerge in pHD and may herald the transition to symptomatic disease. The regional brain correlates of early cognitive impairment in HD have not been well described.

Methods: As part of an ongoing longitudinal progression study in 11 pHD subjects (age 48.1 ± 10.6 ; CAG repeats = 41.6 ± 1.75), we performed comprehensive neuropsychological testing and [^{18}F]fluorodeoxyglucose (FDG) PET. Neuropsychological tests were consolidated into composite scores for attention, working memory, speed of processing, executive function, learning, retention, visual perception, visuomotor construction, fine motor dexterity, and mood. These scores were correlated with brain metabolism in the four regions of a pHD-specific metabolic brain network identified with FDG PET (striatum, anterior cingulate, ventrolateral thalamus, and cerebellum).

Results: Anterior cingulate metabolism correlated with executive function ($r = 0.67$; $P = 0.02$) and fine motor dexterity ($r = 0.83$; $P = 0.003$). Striatal metabolism correlated with visuomotor construction ($r = 0.65$; $P = 0.03$). No other correlations were identified. Over the course of this 4-year progression study, four pHD subjects were diagnosed with HD; at baseline, these subjects exhibited significantly lower performance on tasks of executive function ($P = 0.01$).

Conclusions: Executive function may be abnormal in pHD, especially as pHD subjects near symptom onset. Reduced metabolism in anterior cingulate cortex may underlie early impairments in executive function.

POSTER 10

Correction of Brain Atrophy in Metabolic Imaging of Pre-symptomatic Huntington's Disease: A Combined FDG PET and MRI Study.

Y. Ma, A. Feigin, S. Peng, P. Kingsley, V. Dhawan, and D. Eidelberg. *Feinstein Institute for Medical Research, North Shore-LIJ Health System, USA.*

Background: HD is a hereditary neurodegenerative disorder. Altered regional brain glucose metabolism and atrophy have been reported with [^{18}F]FDG PET and MRI in both presymptomatic HD gene carriers (pHD) and symptomatic patients. It has been suggested that atrophy may contribute to hypometabolism observed in the striatum and the cortex. However, the degree to which brain atrophy accounts for declines in metabolism remains uncertain. In this study, we utilized an atrophy correction algorithm to localize abnormal metabolic changes in pHD subjects as part of a longitudinal study.

Methods: We used PET/MRI brain scans from 12 pHD subjects (CAG length = 42 ± 2 ; age 47 ± 11 years) at baseline and after 18 months. The correction of brain atrophy in each PET image was performed on a voxel basis using registered/segmented MRI data and PET resolution information. Both images were then spatially normalized and separately compared with those from 11 gene-negative normal subjects (age 41 ± 15 years) using statistical parametric mapping. We focused on the effect of brain atrophy on striatal metabolism in this preliminary analysis.

Results: Before atrophy correction, the pHD gene carriers showed progressively significant hypometabolism in the striatum relative to the normal controls. The reduction in metabo-

lism was bilateral and homogeneous in both caudate nucleus and putamen. After atrophy correction, striatal metabolism was normal at baseline but was slightly lower in the posterior putamen at 18 months.

Discussion: Early hypometabolism in pHD is largely accounted for by atrophy. Nonetheless, our data suggest that neuronal dysfunction likely precedes atrophy as HD progresses. The atrophy correction algorithm described here may provide insights into the mechanisms underlying neurodegeneration in HD, and could aid in the development of an imaging biomarker for the disease.

POSTER 11

Plasma 8-OH2'dG As a Diagnostic and Pharmacodynamic Biomarker for HD.

S. Hersch,¹ H.D. Rosas,¹ S. Gevorkian,¹ D. Oakes,² and W. Matson.³ ¹Massachusetts General Hospital, Harvard Medical School, USA, ²University of Rochester Medical Center, USA, and ³Bedford VA Hospital, Boston University, USA.

Background: Oxidative damage to various molecules occurs in HD and likely contributes to neurodegeneration. The addition of a hydroxyl group at the 8 position on guanine bases in DNA, forming 8-hydroxy-2'-deoxyguanosine (8-OH2'dG) is the most common injury, and its accumulation can deleteriously affect transcription. 8-OH2'dG has been detected in the brain of HD patients as well as in HD animal models, and its levels are reduced with neuroprotective antioxidant therapies. Repair of DNA by nucleotide excision (OGG1) results in the release of 8-OH2'dG. Peripherally measured 8-OH2'dG is reflective of DNA damage and repair rates.

Aims: To test the potential for 8-OH2'dG as a diagnostic and pharmacodynamic biomarker of HD.

Methods: 8-OH2'dG levels in the plasma of pre-manifest and manifest subjects with HD and in matched controls were measured using liquid chromatography with electrochemical detection (LCECA). This method allows the determination of femtomole quantities of 8OH2'dG in the presence of nanogram quantities of potential interferences.

Results: 8-OH2'dG is elevated onefold in pre-manifest and more than threefold in early manifest HD. Statistically, 8-OH2'dG levels partially discriminate controls from pre-manifest HD and completely discriminate pre-manifest HD from manifest HD, suggesting that 8-OH2'dG levels may mark the HD prodrome and may mark the transition from pre-manifest to manifest HD. 8-OH2'dG levels also respond pharmacodynamically to treatment with creatine.

Conclusions: 8-OH2'dG levels have potential as a useful diagnostic and pharmacodynamic biomarker for HD. Planning is underway to examine 8-OH2'dG levels in much larger pre-manifest and manifest HD populations in HSG studies.

POSTER 12

HD Repeat Determines the Rate of Neuropathological Change.

T. Massood,¹ J. Latourelle,¹ J. Srinidhi Mysore,² E. Fossale,² T. Gillis,² J.F. Gusella,² M.E. MacDonald,² and R.H. Myers.¹

¹Boston University School of Medicine, USA, and ²Massachusetts General Hospital, Harvard Medical School, USA.

Objective: The purpose of this study was to evaluate whether the rate of change in neuropathological involvement was related to CAG repeat size.

Methods: Medical records were evaluated for 259 post-mortem Huntington's disease brains received from the

Harvard Brain Tissue Resource Center at McLean Hospital in Belmont, MA. Information for ages at motor onset and death was used to determine duration of the disease. Each postmortem brain was graded using the Vonsattel method for evaluating the extent of neuropathological involvement. Brains were available only for grades 2, 3, and 4. HD CAG repeat length was determined for each case at the Center for Human Genetic Research at the Massachusetts General Hospital.

Results and Conclusions: Controlling for duration of disease, for each unit increase in HD CAG repeat an increase of 0.07 units was observed for the neuropathological grade ($P < 0.001$) at death. We compared the average grade for five repeat categories (40–42, 43–44, 45–47, 48–50, and 50+) within four duration groups: brief (<12 years), short (13–17 years), mid (18–23 years), and long (24+ years). Those with shorter repeat sizes had a lower grade of pathological involvement than did those with larger repeat sizes. For example, in the "Mid" duration group, representing a person who died after 18–23 years with HD, those with repeats of 40 to 42 had a mean grade of 2.81, whereas those with repeats of >50 units had a mean grade of 3.83. This indicates that persons with larger repeats had experienced a greater extent of neuropathological involvement than those with shorter repeats over the same time period leading to death. These findings support the hypothesis that the HD repeat size is a powerful determinant of the rate of change in neuropathological involvement.

PRE-MANIFEST STUDIES

POSTER 13

A Study in Pre-Manifest Huntington's Disease of Coenzyme Q10 (Ubiquinone).

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Background: Therapeutic neuroprotective trials in the "pre-manifest" population aimed at delaying the onset of manifest HD could potentially have a significant impact on this devastating disorder. Coenzyme Q10 (CoQ) has emerged as one of the leading therapeutic candidates for neuroprotection in manifest HD [Huntington Study Group, *Neurology* 2001;57:397–404]. Although there are substantial data on the tolerability of CoQ at 600 mg/day in symptomatic HD, dose ranging studies suggest the possibility of decreased tolerability in otherwise healthy individuals at higher dosages.

Proposal: We propose to study CoQ at dosages of 600 mg/day, 1200 mg/day, and 2400 mg/day to determine, in a population of expansion positive pre-manifest participants, the highest dosage that is tolerable, with the long term objective of developing future preventive therapeutic trials of CoQ at that dosage. We propose to establish the safety and tolerability of CoQ at dosages of 600 mg/day, 1200 mg/day and 2400 mg/day in a mutation positive pre-manifest population with the HD CAG repeat expansion, in the context of a randomized double-blind 20 week parallel-group trial. We propose to establish that CoQ is biologically active by assessing changes in serum CoQ levels, as well as 8-hydroxydeoxyguanosine (8OHdG) and 8-hydroxyguanosine (8OHrG) levels in the same trial. We will assess the relationships between serum levels of CoQ, biomarkers of oxidative stress, biomarkers of DNA repair mechanisms (OGG1), and dosage levels of CoQ.

Discussion: The proposed trial is significant in that it will be the first study to evaluate a potential therapeutic agent in a population of individuals at 100% risk for developing a neurodegenerative illness, but who are not yet ill. It will allow us

to select a dosage of CoQ for future definitive randomized placebo controlled trials in pre-manifest HD to delay or prevent onset of manifest HD, and will give us valuable information about the process and feasibility of such trials in pre-manifest participants.

POSTER 14

Recruitment and Retention Strategies for PREDICT-HD Study at HSG Site 144.

O. Yastrubetskaya, J. Preston, and E. Chiu. *The University of Melbourne, Australia.*

Aims: Report successful recruitment and retention strategies used by St George's Huntington's disease clinic in a prospective international study, PREDICT-HD–Neurobiological Predictors of Huntington's Disease.

Methods: Review of source documents of PREDICT-HD participants. Review of screening and study retention rates. Outline selection, recruitment and retention strategy and identify the most effective practices.

Results: Over 4 years (July 2003–July 2007), 99 subjects were screened and 76 enrolled. Enrollment success rate: 77%; retention rate: 93%. Of 76 subjects, 30 (39%) are members of 12 families participating at our site; 46 subjects (61%) do not have participating relatives.

Key recruitment strategies: Long-standing (over 30 years) relationship with HD community, close collaboration with AHDA and the HD community, and prompt and efficient response to potential and enrolled participants.

Key retention strategies: 1) Visits scheduled for times and dates convenient for participants and their companions. 2) Minimized transportation and accommodation 'hassles.' 3) Welcoming and supportive environment. 4) Value-added quality of life and lifestyle services. 5) Regular communication between visits, including Christmas greetings.

Discussion: The St George's Clinic operated by the Academic Unit has very high rates of enrollment and retention success. This is achieved by the application of number of strategies, including study promotion through AHDA, direct marketing to the HD community, and careful selection process. Successful retention is achieved by sensitive rapport building, support, regular communication, and personal relationships with participants by designated team member. Encouragement of value added activities during visit. The effective strategies utilized by the Academic Unit resulted in successful participation in PREDICT-HD (the highest recruiting center of the 32 centers) and thus contributes to the development of body of knowledge about HD for the benefit of current and future HD community members.

POSTER 15

PREDICT-HD Family Participation in HSG Site 144.

O. Yastrubetskaya, A. Goh, J. Preston, and E. Chiu. *The University of Melbourne, Australia.*

Background: HD research is impossible without the dedicated support of participants and their families. Due to the low prevalence and incidence of HD in the population, recruitment is challenging. The PREDICT-HD study commenced in 2003 at the St George's site, operated by the Academic Unit. It is the leading recruitment site, with 99 potential participants screened and 76 enrolled (77%). Family members share the awareness of the research through 1) regular updates, telephone calls, and newsletters from the site; 2) letters of thanks and information sent to participants; 3) family communication; and 4) AHDA meetings and newsletters.

Methods: We analyzed our PREDICT-HD cohort and familial relationships, determining the number of families with one participating member, families with multiple participating members, the number of first and second-degree relatives, of gene-positive and gene-negative participants, and the number of other family members who are eligible to participate in the study.

Results and Discussion: Of 76 subjects, 30 (39%) are members of 12 families with more than one PREDICT-HD participant participating at our site. Family genograms and analysis of first- and second-degree relatives will be presented. The timeframe of enrollment of family members was highly variable—from months to years.

Overall, family participation is high at our site, but the timeframe of enrollment was found to be highly variable. The high rate of family participation reflects a strong family commitment to HD research and has significantly contributed to the data.

Recruitment and retention strategies are necessary to maintain such high levels of family participation.

POSTER 16

Influence of Insurance on the Decision to Pursue Genetic Testing in Individuals at Risk for Huntington's Disease.

E. Oster,¹ E.R. Dorsey,² J. Bausch,² A. Shinaman,² E. Kayson,² D. Oakes,² I. Shoulson,² K. Quaid,³ and the Huntington Study Group PHAROS Investigators. ¹*The University of Chicago, USA,* ²*University of Rochester Medical Center, USA,* and ³*Indiana University, USA.*

Background: The frequency of genetic testing among individuals at risk for Huntington's disease (HD) is low, despite potential advantages to knowing one's HD gene status.

Aim: To explore insurance-related barriers to genetic testing and to evaluate factors associated with the eventual pursuit of testing in a PHAROS, a longitudinal observational study of asymptomatic individuals at risk for HD [Arch Neurol 2006; 63:991–996].

Methods: We used PHAROS data to explore the reasons cited for lack of genetic testing at enrollment in the study. We also compared the pre-testing survey responses of those who pursued testing and those who did not.

Results: All 1001 individuals enrolled in PHAROS had some data available at enrollment. At baseline, 54% of those enrolled report that fear of insurance loss was either a "somewhat" or "extremely" important factor in their decision not to pursue genetic testing thus far. Only 13% ranked this factor as an "extremely unimportant" barrier to testing. Relative to individuals who did not pursue testing, those who did viewed insurance loss as an initial barrier to testing ($P < 0.01$). Individuals who were eventually tested were also significantly more likely to have paid out of pocket for insurance costs, to avoid revealing their genetic risk (20% vs 3%, $P < 0.001$). Items paid for out of pocket were principally baseline screening for neurological problems and for pre-implantation genetic diagnosis.

Conclusions: Fear of insurance loss appears to be a significant barrier to genetic testing for individuals at risk for HD. Paying health care expenses out of pocket to avoid revealing risk status is a reality for a significant fraction of people at risk.

POSTER 17

Living at Risk: Concealing Risk and Preserving Hope in Huntington's Disease.

K. Quaid,¹ S. Sims,² M. Swenson,² J. Harrison,³ C. Moskowitz,⁴ N. Stepanov,⁵ G. Suter,⁶ B. Westphal, and the Huntington Study Group PHAROS Investigators. ¹*Indiana University*

School of Medicine, USA, ²Indiana University School of Nursing, USA, ³Emory University School of Medicine, USA, ⁴Ohio State University, USA, ⁵Hereditary Neurological Disease Center, USA, and ⁶Hennepin County Medical Center, USA.

Background: The Prospective Huntington At Risk Observational Study (PHAROS) is a longitudinal observational study of 1001 individuals at risk for Huntington's disease (HD) who have chosen not to be tested for the presence or absence of the genetic mutation that causes HD.

Aim: To explore the everyday experience of living while at risk for HD in a group of individuals who have chosen not to be tested.

Methods: Fifty-five in-depth qualitative interviews were conducted at six different PHAROS sites in the United States.

Results: The experience of living at risk was the overarching pattern demonstrated in these data. Two foundational themes emerged: 1) careful concealment of one's status of being at risk as an act of self-preservation and 2) not being tested as a way of preserving hope for the future. Quotations from interviews will be presented to illustrate these two major themes.

Conclusions: Individuals at risk for HD make complicated decisions about whether or not to share the fact of their genetic risk and with whom to share this information. In the absence of a treatment or cure, many individuals view the decision not to undergo genetic testing as a way of preserving their sense of hope for the future. These data illustrate the importance of ensuring that the decision whether or not to undergo genetic testing remains a free and autonomous choice of the individual at risk.

POSTER 18

Sensitivity of the UHDRS Cognitive Tests in Pre-Diagnosis and Early Huntington's Disease (HD).

A. Tomusk,¹ S. Queller,¹ S. Lifer,¹ S. Hastings,¹ J. Dawson,¹ B. Walker,¹ K. Whitlock,¹ and J.C. Stout.² ¹Indiana University, USA, and ²Monash University, Australia.

Aims: The cognitive component of the Unified Huntington's Disease Rating Scale (UHDRS), which includes the Stroop Color-Word Interference Test, Controlled Oral Letter Fluency, and Symbol Digit Modalities Tests (SDMT), was developed and validated on patients with moderate to severe HD [Huntington Study Group, *Mov Disord* 1996;11:136-142], and more recently has been used extensively in pre-diagnosis and early HD. We used meta-analysis to examine the relative sensitivity of each of the UHDRS cognitive tasks in these earlier phases of HD.

Methods and Results: First, we conducted a systematic review of the literature published since 1993 (advent of PCR genetic analysis) to identify 38 studies that 1) compared test performance in pre-diagnosis or early HD (<7 years since diagnosis) longitudinally over time or cross-sectionally to a gene-negative control group and 2) contained sufficient data on a UHDRS cognitive test to compute an effect size (ES). Using meta-analysis to estimate ESs (Hedge's *g* for cross-sectional studies and standard paired difference for longitudinal studies), the largest ESs were found in cross-sectional studies of early HD (*g* ranging from -1.04 to -1.58; $P < 0.001$ across all tests). In contrast, cross-sectional studies in pre-diagnosis HD indicated statistically significant ESs only for the Word and Color conditions of the Stroop ($g = -0.48$, $P < 0.01$, and $g = -0.49$, $P = 0.01$, respectively) and Letter Fluency ($g = -0.38$; $P = 0.02$), with larger ESs being associated with increasing proximity to onset. There were few longitudinal studies; among

these, only the Word and Color conditions of the Stroop and the SDMT showed significant decline in pre-diagnosis HD.

Conclusions: The SDMT and Stroop Word and Color conditions show the greatest longitudinal decline in pre-diagnosis HD and as such are the best candidates from the UHDRS cognitive battery for use as outcome measures in clinical trials.

POSTER 19

Longitudinal Decline in Negative Emotion Recognition Prior to Diagnosis in Huntington's Disease.

S.A. Johnson,¹ J.C. Stout,^{2,3} S. Queller,² K. Whitlock,² D. Langbehn,⁴ E. Aylward,⁵ J. Paulsen,⁴ and the PREDICT-HD Investigators of the Huntington Study Group. ¹Dalhousie University, Canada, ²Indiana University, USA, ³School of Psychology, Psychiatry and Psychological Medicine, Monash University, Australia, ⁴University of Iowa, USA, and ⁵University of Washington, USA.

Background: The PREDICT-HD study is a prospective, longitudinal study of cognitive, psychiatric, motor, and brain changes in the pre-manifest stages of Huntington's disease (HD). In contrast to prior reports of a disgust-specific emotion recognition deficit in HD, the baseline data from the PREDICT-HD study indicated that CAG-expanded individuals not yet meeting criteria for clinical diagnosis (preHD) demonstrated significantly less accurate recognition of all negative emotions (anger, disgust, fear, sadness), compared with CAG-unexpanded controls [Johnson et al., *Brain* 2007; 130(Pt 7):1732-1744].

Methods: In the current study, we examined the same computerized facial emotion recognition task across a 2-year longitudinal interval in 407 participants (361 preHD and 46 controls). Logistic regression with repeated measures was used to examine associations between 2-year change in emotion recognition performance and measures of estimated proximity to clinical diagnosis (based on CAG repeat length and current age), striatal volumes, and motor signs of HD.

Results and Discussion: Overall, the longitudinal findings were consistent with our cross-sectional results. Two-year declines in recognition of anger, disgust, fear, and sadness (but not happiness and surprise) were associated with estimated proximity to clinical diagnosis. Baseline striatal volumes were predictive of the amount of 2-year decline in recognition of happy and fearful faces, and 2-year change in striatal volume was associated only with the amount of decline in fear recognition. Interestingly, we found no association between baseline motor signs of HD, characterized by the UHDRS confidence level ratings, and 2-year change on the emotion recognition task. Findings confirm our cross-sectional conclusion that recognition of all negative emotions declines early in the disease process in HD and, furthermore, reveal that the rate of decline is fastest for those estimated to be closest to clinical onset.

POSTER 20

Abnormal Structure of Cerebral White and Cortical Gray Matter in Preclinical Huntington's Disease.

P. Nopoulos, J. Paulsen, L. Beglinger, H. Johnson, V. Magno, R. Pierson, D. Langbehn, and the PREDICT-HD Investigators and Coordinators of the Huntington Study Group. *University of Iowa Carver College of Medicine, USA.*

Introduction: The pathoetiology of Huntington's disease (HD) is known classically as involving primarily the striatum. Recent studies, however, have emphasized the involvement of additional brain regions, such as the cerebral cortex and white matter. This study was designed to assess the structure (vol-

ume) of the cerebral cortex and white matter in a large group of subjects with preclinical HD.

Methods: A total of 612 subjects had MRI scans, collected from the multicenter PREDICT-HD study; 128 gene-negative subjects served as controls for 484 gene-expanded subjects. The gene-expanded subjects were divided into 30 with recent diagnosis and three prognostic groups not yet diagnosed: far from, midway to, and near HD onset (based on CAG length and age). Volumes of cerebral cortex and white matter were expressed as ratios to intracranial volume. Age, gender, and scanner-to-scanner variation were statistically controlled.

Results: Cortical volumes were slightly lower than the control group for all three preHD groups. Although statistically significant, differences were subtle and did not show substantial change among the far, mid, and near groups. Furthermore, no clear change was shown for those recently diagnosed. In contrast, cerebral white matter volume was robustly different, with the far from onset preHD group having smaller volumes relative to the comparison group ($P = 0.0006$), and with progressively lower white matter volumes seen in subsequent groups: far > midway > near onset > recently diagnosed.

Discussion: In preclinical HD subjects, white matter volumes are significantly decreased, even far from disease onset. In contrast, global cortical volume changes are relatively small. Measurable progression of smaller white matter volume spanning many years from diagnosis through recent diagnosis supports the notion that these changes could potentially be utilized as a biomarker for disease progression.

MANIFEST-HD STUDIES

POSTER 21

Late-Onset Huntington's Disease: A Review of 41 Cases.

H. Lipe and T.D. Bird. *VA Puget Sound Health Care System and University of Washington, USA.*

Our HD specialty clinics have followed more than 40 individuals with onset of HD at age 55 or older. This review presents a compilation of these cases seeking unique characteristics of this subpopulation. Symptoms at onset, delay in diagnosis or misdiagnosis, CAG repeat expansion size, whether the older person is the first in the family to be diagnosed with HD, social issues, course of the disease, and co-morbidity (including Alzheimer's disease) are tabulated. Implications for genetic counseling are discussed.

POSTER 22

Huntington's Disease: Causes and Place of Death in a Closely Followed Population.

E.A. McCusker and A. Lownie. *Westmead Hospital, Australia.*

Objective: Review cause and place of death in Huntington's disease (HD) patients followed up in the community.

Background: HD has a prolonged course of up to 17 years, often longer. Death is usually in an institution when hospital-based clinic follow-up may be impractical. The number of patients known to the HD service in New South Wales is similar to the estimated prevalence in the state of New South Wales. There is a need for more information about the place and cause of death to allow improved chronic and palliative care.

Methods: Review of confidential data base and service records January 1996–June 2005 for patients known to the

comprehensive multidisciplinary HD service based at Westmead Hospital in Sydney that allows contact with and follow-up for most patients in the state of New South Wales over the course of HD. Demographic data and place and cause of death were analyzed.

Results: Of 450 HD patients followed over almost 10 years, 150 died, most in an institution. Mean life span was 59 years (range 25–90). 128 resided in institutions. Cause of death was known in 98. Inanition and gradual deterioration were most frequent, accounting for 43 deaths. Death resulted from pneumonia in 23. Head injury was the cause in 8. No death was due to choking. There was a low rate of 4 suicides.

Discussion: This population, followed in the community until death, was equivalent in number to the known estimated prevalence for HD in the state of NSW and may therefore more accurately reflect the causes of death in HD. The low suicide rate of 1% may be attributable to the close monitoring of this group in the HD clinic as well as within the community.

POSTER 23

How People With Huntington's Disease Die: A Survey.

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Objective: To describe the symptoms of the last year of life for Huntington's disease patients residing in a skilled nursing facility.

Methods: This study was a chart review of 11 Huntington's disease patients who died at Terence Cardinal Cooke Health Care Center between 1996 and 2003. The reviews were conducted after death, and chart selection was based on chart availability. The following information was reviewed: progress notes and physician's orders for the last year of life, intake assessments, advance directives, genetic testing reports, and demographic data.

Results: The mean age at admission was 44.8 years, and the mean age at death was 51.2 years. The mean age of onset was 39.4 years, and the mean disease duration was 12.8 years. The number of unique prescriptions was 13.82, and the number of medications decreased exponentially as the length of stay increased. PEG tube replacement was the most frequent reason for hospital transfer. The average number of hospitalizations was 4.1, and the number of hospitalizations was inversely correlated with length of stay. As length of stay increased, difference between maximum and minimum weight decreased significantly. Seven of the 11 patients had recorded decreases in net annual weight change. Nine patients were on feeding tubes, four were independently mobile (during at least part of the last year of life), and five retained verbal capacity. Seven patients had at least one advance directive in place. Four patients had suspected diagnosis or confirmed diagnosis of aspiration pneumonia at death. Other recorded circumstances of death included cardiac arrest, cancer, found unresponsive/no pulse, and lethargy.

Conclusions: The last year of life in HD is idiosyncratic, defying accurate prognostication. Although most patients will become a verbal and immobile in the end stages, death can occur unexpectedly in higher functioning residents, which complicates discussions relating to terminal care.

BASIC SCIENCE/EXPERIMENTAL THERAPEUTICS

POSTER 24

The MLK Inhibitor, CEP-1347, Suppresses Mutant Huntingtin-Associated Neurotoxicity in Cell, *Drosophila* and Mouse Models of HD by Modulating MAPK Signaling and Upregulating Brain Derived Neurotrophic Factor.

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Background: We have previously reported that mutant Htt activates mitogen-activated protein kinase (MAPK) signaling, including the extracellular signal-regulated protein kinase (ERK1/2) and c-Jun N-terminal kinase (JNK) pathways [Apostol et al., Hum Mol Genet 2006;15:273–285]. Chemical and genetic modulation of these pathways promoted cell survival and death, respectively.

Methods: In this study we tested the ability of two closely related mixed-lineage kinase (MLK) inhibitors, CEP-11004 and CEP-1347, which target upstream of JNK, to suppress mutant Htt-mediated pathogenesis in multiple Htt-expressing cell lines and in vivo in *Drosophila* and R6/2 mouse models of HD.

Results: As expected, CEP-11004/CEP-1347 treatment significantly decreased toxicity in mutant cells that demonstrate a strong JNK response. However, suppression of cellular dysfunction in cell lines that exhibit only mild Htt-associated toxicity and little JNK activation was associated with activation of ERK1/2 in an MLK-independent manner. Treatment of other HD models with these compounds, including immortalized striatal neurons from mutant knock-in mice and *Drosophila* spp. expressing a mutant Htt fragment, also produced striking protection against neurotoxicity. Finally, R6/2 mice treated with CEP-1347 showed a significant improvement in motor behavior. This protective effect was not associated with a reduction in JNK activation in the brain, but rather with an increase in expression of BDNF, a potential downstream target of ERK1/2 and a critical neurotrophic factor reduced in HD.

Conclusions: These studies suggest that pharmacologic intervention in MAPK signaling may be an appropriate approach to HD therapy and that CEP-1347, shown to be well tolerated in human clinical trials, is a potential therapeutic option.

POSTER 25

Discovery and Development of Novel HDAC Inhibitors for Huntington's Disease.

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Background and Objectives: Several lines of experimental evidence suggest that transcriptional dysregulation mediated by histone acetyl transferases plays a role in the pathology of Huntington's disease (HD). One approach to treating HD is to counteract such dysregulation by inhibiting histone deacetylases (HDACs). Currently available HDAC inhibitors (HDACi's) display weak potency and selectivity (e.g., sodium butyrate, valproic acid), do not penetrate brain well after systemic administration (e.g., suberoylanilide hydrox-

amic acid [SAHA]), or display genetic toxicity (trichostatin A [TSA]). We therefore initiated an effort intended to discover and develop potent, orally bioavailable, and brain-penetrant HDACi's.

Results and Discussion: We now report on Compound 3, which is being considered for preclinical development. Compound 3 was profiled against a panel of human recombinant HDAC isoforms and displayed selective inhibition of a subset with nanomolar IC₅₀ values. Compound 3 inhibits HDAC activity in whole cells (mouse cortical neurons, human astrocytes, HEK293 cells) with IC₅₀ values ranging from 0.3 to 1 μ M. In mice, oral administration of Compound 3 results in increased acetylation of histones 2A, 3, and 4 in mouse striatum with a minimal effective dose (MED) of 10 mg/kg. Oral bioavailability is 37% in mice and 45% in dogs, with a terminal half-life of 2 and 0.5 hours, respectively. Compound 3 is negative in standard genetic toxicity assays. The compound has been administered to mice for 14 days at doses >10-fold the MED with minimal untoward effects and no negative histopathological findings. Compound 3 is undergoing efficacy testing in the R6/2 transgenic mouse model of HD.

METHODOLOGICAL STUDIES

POSTER 26

A Scale To Measure Quality of Life in Huntington's Disease Spousal Carers.

A. Aubeeluck and H. Buchanan. *University of Nottingham, United Kingdom.*

Objective: The purpose of this series of studies was to systematically investigate the factors that enhance and compromise the lives of Huntington's disease (HD) spousal carers by utilizing the theoretical construct of quality of life (QoL).

Methods and Results: Three exploratory studies provided evidence that spousal carers of HD patients have specific difficulties in maintaining their QoL while continuing in a primary care-giving role. Study 1 provided preliminary evidence that spousal carers of HD patients and health care professionals would value a disease-specific QoL scale that could be used to evaluate the spousal carer's objective and subjective QoL. Study 2 established that spousal carers of HD patients often experience loneliness, a need to escape, and a unique sense of loss, while trying to adequately care for their loved ones and maintain some form of QoL for themselves. Study 3 provided further evidence that QoL is compromised in many ways and is an issue for HD carers. The carers in this study often neglected their own needs as the care-giving role and disease processes 'took over' their lives as well as the life of the HD-affected spouse.

The findings of these three studies prepared the way for the development of a disease-specific QoL measure for spousal carers of HD patients. Validation of the Huntington's Disease Quality of Life Battery for Carers (HDQoL-C) was performed in study 4. The HDQoL-C was established as a multidimensional and psychometrically sound disease-specific and subjective QoL assessment tool that incorporates the individual's physical health, psychological state, level of independence, social relationships, personal beliefs, and relationship to salient features of the environment. It demonstrates good internal consistency, test-retest reliability, and face validity. Although it was developed with a UK population, we intend to validate the HDQoL-C for use with a North American population in order to implement and assess therapeutic interventions.

POSTER 27

A Model of the Extent and Impact of Inter-Rater Variability for the UHDRS Motor and Diagnostic Confidence Scales.

D.R. Langbehn,¹ J.S. Paulsen,¹ C. Ross,² K. Biglan,³ and B. Landwehrmeyer.⁴ ¹University of Iowa, USA, ²Johns Hopkins University, USA, ³University of Rochester Medical Center, USA, and ⁴University of Ulm, Germany.

Background: The UHDRS99 scales for Huntington's disease motor signs and diagnostic confidence constitute nearly universal research standards. Despite their great utility, analyses from the PREDICT-HD study suggest substantial variation in scale calibration among expert raters. Improved standardization would yield improved statistical power and replicability of clinical HD studies, including therapeutic trials.

Methods: We approximated differences between current scale use and ideal standardization by fitting Cox proportional hazard models predicting time until diagnosis (by UHDRS diagnostic confidence rating = 4) as a function of either baseline UHDRS total motor score or diagnostic confidence rating. We fit these models with and without a random ("frailty") effect for variability among motor-raters in their propensity to assign new diagnoses. If the raters' calibrations of diagnosis, lesser diagnostic confidence levels, and motor scores are linked, then adjustment for this rater effect approximates the potential impact of ideal standardization on the prognostic value of baseline motor ratings and confidence levels.

Results: Of 551 gene-expanded PREDICT participants, 68 received prospective diagnoses. Median follow-up was 2 years. Preliminary analyses showed substantial variability in motor scores at the time of diagnosis among 47 raters. Random inter-rater variability was highly significant in proportional hazard models based on either baseline motor score or diagnostic confidence ($P < 0.0001$ in each case). Motor scores and diagnostic confidence were substantially more predictive in the models adjusted for inter-rater variability. The proportional hazard (PH) effect of a 5-point motor scale difference was 42% stronger in the rater-adjusted model. PH effects for initial diagnostic confidence increased between 14% (confidence level 1 vs 0) and 86% (confidence level 3 vs 0).

Conclusions: Although these analyses cannot entirely clarify the relative importance of motor score *versus* diagnostic confidence standardization, they highlight the potential value of improved, systematic rater training for both scales.

POSTER 28

Item Reduction of the University of Pennsylvania Smell Identification Test: Preparation for Clinical Trials in Pre-HD using the PREDICT-HD Cohort.

K.B. Whitlock,¹ J.C. Stout,^{1,2} S. Queller,¹ D.R. Langbehn,³ N.E. Carlozzi,¹ J.S. Paulsen,³ and the PREDICT-HD Investigators of the Huntington Study Group. ¹Indiana University, USA, ²School of Psychology, Psychiatry and Psychological Medicine, Monash University, Australia, and ³University of Iowa, USA.

Background: In order to prepare for clinical trials in Huntington's disease (HD), there is a need to identify sensitive markers that reliably track disease progression during the earliest phases of the disease (prior to clinical diagnosis; pre-HD).

Methods: In the PREDICT-HD study, we have identified the University of Pennsylvania Smell Identification Test (UPSIT) as one of several sensitive markers. The UPSIT, which takes up to 20 minutes administration time, requires participants to identify 40 different scratch-and-sniff smells (10 items in each of 4

books) by matching the smell to one of four possible choices. Despite the UPSIT's demonstrated cross-sectional and longitudinal sensitivity in pre-HD individuals, its lengthy administration time limits its utility in interventional trials. To examine the possibility of reducing administration time by reducing the number of items, we computed 2-year longitudinal effect sizes for pre-HD participants and controls for each of the four books, for two published alternative books (one 10-item and one 12-item book), and for pairs of these books. We also examined the ability of each of these test books and for pairs of test books to predict class membership (pre-HD; near, mid, and far from clinical diagnosis; and controls).

Results: Although the general patterns of effect sizes were consistent across books, the combination of books 1 and 3 yielded effect sizes that were most similar in magnitude to the effect sizes for the full four-book test. Furthermore, all books yielded similar group classification accuracy.

Conclusions: On the basis of our findings, we recommend using a 20-item abbreviated version of the UPSIT (books 1 and 3) in clinical trials with pre-HD participants. This abbreviated version will substantially shorten administration time without sacrificing the overall sensitivity of this test to subtle disease progression in pre-HD.

POSTER 29

Candidates for Neurocognitive Markers in PRE-HD: Longitudinal Assessment From the PREDICT-HD COHORT.

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Background: Many studies have demonstrated declines in cognitive functions prior to the clinical onset of HD (pre-HD); however, insufficient longitudinal data has been available to allow the development of a cognitive assessment battery with known sensitivity for intervention trials in pre- and early HD. The PREDICT-HD cognitive battery has been examined longitudinally in more than 400 CAG-expanded participants and controls.

Methods: This presentation reports longitudinal results from the cognitive assessment component of PREDICT-HD, following examination of 175 variables in three pre-HD groups based on their estimated proximity to onset: NEAR (≤ 9 estimated years to onset, $n = 113$), MID (between 9 and 15 estimated years, $n = 120$), and FAR (≥ 15 estimated years, $n = 114$). Groups are compared on standardized rates of change in cognitive performance over 2 years, controlling for age, education, gender, and pre-morbid IQ.

Results: Cognitive decline over time was significant for those nearer to onset for several cognitive variables (2-year longitudinal effect sizes ranged from ~ 0.2 to ~ 0.8 standard deviations of change). Furthermore, when the cognitive variables are considered simultaneously, it is possible to identify variables that make independent contributions and variables that are redundant with other cognitive variables in the PREDICT-HD cognitive battery.

Conclusions: Discussion of these results will include an initial description of a cognitive assessment battery with known sensitivity for pre-HD, based on findings from PREDICT-HD, along with a strategy for the continued development of a cognitive assessment with further enhanced utility for intervention trials in pre-HD.

POSTER 30

Proposed Criteria for the Diagnosis of Dementia Associated With Huntington's Disease (HD).

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Objective: To develop criteria for more accurate diagnosis of HD dementia by identifying specific cognitive deficits that contribute to functional impairment.

Background: Criteria for HD dementia have been based largely on features of Alzheimer's disease (AD), which includes memory loss as an essential element. Functional impairment in HD, however, is often caused by other cognitive deficits that occur well before memory problems arise.

Methods: We administered the UHDRS Functional Independence Scale (FIS) in addition to neuropsychological tests to a group of 84 HD subjects representing a broad range of functional abilities. Using the DSM-IV requirement for a decline from a previous higher level of functioning to define dementia, we identified the cognitive measures most likely to account for variance in functional capacity, as measured by the FIS, using regression analyses.

Results: Of the 84 subjects, 58 were coded as functionally impaired (FIS $\leq$ 80) and 26 as functionally intact. In the linear regression, Stroop Color Naming (speed of processing) and the Mattis DRS Initiation subscale (executive function) accounted for 68.0% of the variance in the FIS. The DRS Memory subscale accounted for no additional variance. The logistic regression revealed that the Stroop and DRS Initiation measures correctly classified 89.3% of subjects as functionally impaired or intact. These results were unchanged even when measures of motor functioning (i.e., dysarthria, eye movements, bradykinesia) were included in the regression.

Conclusions: HD dementia differs from that associated with AD in that memory loss is not a salient feature, as other cognitive domains make a significantly greater contribution to functional impairment. We propose a definition of HD dementia that includes demonstrable evidence of impairment in speed of processing and deficits in at least one additional area of cognition (e.g., attention, executive function, visuospatial ability, memory) in the context of impaired functional abilities and a deteriorating course.

POSTER 31

Controlling for Individual Differences in Neurocognitive Markers in Pre-Diagnosis HD in the PREDICT-HD Cohort.

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Background: Prior to clinical diagnosis, individuals with the CAG expansion for Huntington's disease demonstrate subtle impairment on a number of neurocognitive tests relative to individuals without the CAG expansion. To enhance the detection of such subtle differences in performance, it is possible to statistically control for variation in IQ, age, and other individual difference variables. However, controlling for variables that change in concert with disease progression will obscure detection of disease-related declines in cognition.

Methods: In the PREDICT-HD cohort ($N \approx 880$ for cross-sectional and $N \approx 450$ for longitudinal analyses) we identified potential covariates by correlating baseline values of demographic

variables, estimated IQ, levels of depression, and expertise variables with 1) performance on 20 neurocognitive tasks, 2) the 2-year change in performance on the same neurocognitive tasks, and 3) baseline estimates of disease progression, including probability of clinical onset, motor scores, and striatal volumes.

Results: Baseline values of age, gender, education, estimated premorbid IQ, depression, and music or typing expertise were related to the majority of the neurocognitive performance measures at baseline, but mostly unrelated to 2-year change in neurocognitive measures.

Discussion: These results suggest that it is necessary to statistically control for individual differences in demographics, estimated IQ, depression, and expertise, or risk obscuring subtle neurocognitive differences in cross sectional studies. In contrast, 2-year changes in neurocognitive measures were largely unaffected by individual differences in baseline values of demographics, estimated IQ, depression, and expertise, suggesting that it may not be necessary to control for these individual differences in longitudinal analyses. Furthermore, because 1) age is used in conjunction with CAG-expansion to calculate the probability of clinical onset for each participant and 2) age is confounded with indices of disease progression, including age as a covariate in analyses may be overly conservative, whereas not including it may result in overestimation of disease-related changes.

POSTER 32

A Comparison of Two Brief Cognitive Screening Instruments in Huntington Disease (HD).

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Objective: To compare the utility of two brief screening measures to detect cognitive impairment in individuals with HD.

Background: The most commonly used brief screening instrument for cognitive impairment is the Mini-Mental State Exam (MMSE). HD patients, however, often score at or near ceiling on this measure. The Montreal Cognitive Assessment (MoCA), designed as a rapid screening instrument for the detection of mild cognitive impairment, contains the same number of total points as the MMSE, but more items pertaining to attention and executive functioning, areas known to be affected in HD.

Methods: The MMSE and MoCA were administered on the same day in counterbalanced order to 27 individuals (mean age = 51 years; mean CAG repeat length = 44.6) diagnosed with HD. Differences on the two cognitive screening measures were examined using repeated measures ANOVA.

Results: Scores on the MMSE ($M = 25.0$) were consistently higher than those on the MoCA ($M = 20.4$). Notably, every subject's score on the MoCA was either the same or lower than their score on the MMSE. A repeated measures ANOVA revealed a significant difference in performance on the two measures ($P < 0.001$). Sixty-three percent of the HD subjects lost points on the MoCA in executive functioning, an area that is not adequately assessed by the MMSE. Attention scores differed, too, with 63% of subjects losing points on the MoCA and only 22% on the MMSE ($P = 0.006$). In addition, a greater percentage of subjects lost points on the memory portion of the MoCA than the MMSE (81% vs 33%, $P \leq 0.001$).

Conclusions: Our results suggest that the MoCA, with its greater focus on attention and executive functioning, may be more effective than the MMSE as a brief screening instrument for detecting cognitive impairment in individuals with HD. Larger studies will be needed to confirm and extend these findings.

LATE-BREAKING RESEARCH

POSTER 33

Genetic Testing for the Huntingtin Gene CAG Repeat Comparing DNA from Buccal Swabs with DNA from Peripheral Blood.

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Background: Extraction of DNA for genetic testing using buccal cells collected by sterile swab or by mouthwash is a well-established method. Sterile swabs for buccal cell collection and reliable kits and protocols for extraction of DNA from buccal cells are readily available. For patients, obtaining DNA from buccal cells has obvious advantages over the use of peripheral blood, especially in individuals with movement disorders: it is less invasive and more comfortable for the patient, entails fewer risks of infection or bruising, does not require a licensed phlebotomist, and does not require a hospital or clinic setting for collection.

Method: With permission of the UCSD Human Research Protection program, we collected specimens of buccal cells and peripheral blood from 17 individuals at risk for Huntington's disease (HD). DNA was extracted from buccal cells collected with a sterile swab and from peripheral blood by using the Puregene DNA isolation kit and associated protocols (Gentra Systems). PCR primers were end-labeled with ³²P. DNA was amplified by PCR and then sized on an acrylamide gel by using published methods. We compared the CAG repeat sizes we obtained from each source of DNA for each individual.

Results: Ten females and seven males at risk for HD were studied. Average age was 44 ± 9.1 years. Fourteen individuals had an expanded CAG repeat, ranging from 42 to 59 repeats (median 44 repeats). Three individuals had CAG repeat alleles within the normal range. There was complete concordance between CAG repeats for each individual studied, comparing DNA from buccal cells versus DNA from peripheral blood.

Conclusion: DNA extracted from buccal cells can be amplified and accurately sized to determine the HD CAG repeat sizes.

POSTER 34

Treatment of HD: A Survey of HD Clinicians.

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Objective: To determine treatment patterns for the clinical manifestations of Huntington's disease (HD) among a worldwide consortium of individuals who specialize in HD.

Background: There has been relatively little clinical investigation of the treatment of motor and behavioral manifestations of HD. Despite recent trials reporting the efficacy of treatments for motor symptoms (e.g., tetrabenazine), there are few clinical trials of behavioral problems. Because behavioral aspects can be a source of significant disability for HD patients and their families, more information on treating behavior is needed.

Methods: We conducted a survey among HD investigators and

coordinators from the Huntington Study Group (HSG) and the European HD Network (EHDN). The study was completed via a Web-based survey. All responses were anonymous. The survey consisted of questions regarding preferred treatments for motor and psychiatric symptoms of HD.

Results: A total of 262 individuals (104 investigators, 158 coordinators) were sent the survey; 82 responses (31%) received. Treatment of chorea is quite diverse, with tetrabenazine (36%), haloperidol (28%), amantadine (28%), and olanzapine (25%) reported as first choice agents. The majority of clinicians (64%) do not treat dystonia. SSRIs are first-line agents for depression (90%), but NSRIs (68%) are also used initially. SSRIs remain the first-choice agent for anxiety. Benzodiazepines are used only after failed treatment with SSRIs. No specific SSRI emerged for treating depression or anxiety. Anticonvulsant agents are commonly used to treat irritability/agitation. Atypical neuroleptics are commonly used to treat psychotic symptoms; however, no specific agent emerged as a preferred medication. Apathy tends to not be treated pharmacologically.

Conclusions: Treatment of HD symptoms is varied. Tetrabenazine is preferred for motor symptoms despite the fact that it is not available in the USA. SSRIs are preferred for anxiety and depression. Atypical neuroleptics are used for agitation and psychotic symptoms. No specific agent emerged for treating any behavioral symptoms. Controlled clinical trials are necessary to better identify treatment of neuropsychiatric symptoms in HD.

POSTER 35

Communicating Findings to Research Participants: Preliminary Results from the TREND-HD Study.

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Background and Aim: Communicating findings of clinical trials to research participants is infrequently accomplished in a systematic or timely fashion. We sought to evaluate the effectiveness of a concerted communications effort in TREND-HD, an industry-sponsored, multicenter trial of ethyl-EPA for Huntington disease conducted by the Huntington Study Group (HSG).

Methods: We developed a plan to communicate study findings that included (1) a media release from investigators within a day after a sponsor-issued press release; (2) a subsequent telephone call from site staff to participants; and (3) a conference call with the sponsor for all participants two weeks after release of the results. We conducted a postal survey of research participants to determine how and when they learned the research results and their level of satisfaction with the communication plan.

Results: To date, 25 of the 42 sites have participated in the survey, accounting for 200 (63%) of the 316 research participants. One hundred (50%) responded. Respondents were older (56.1 vs 51.3; $P < 0.001$) and had higher total functional capacity (10.2 vs 9.6; $P = 0.04$) than non-respondents. Most respondents (71%) first learned of the study results from their

site phone call, and 58% learned the results within two days of the sponsor's press release. Participants reported high satisfaction with the phone call (89% were either satisfied or completely satisfied) and the conference call (84%) but relatively low satisfaction (46%) with the press release. About 80% of respondents reported good understanding of the risks and benefits of the intervention and the next steps for their participation. Most respondents (60%) preferred that results undergo a thorough review before their being informed of them, even if the review delayed their learning of the results.

Conclusions: In this study, responding research participants learned the findings of the study soon after public release and they highly valued the personalized communication efforts by the study investigators.

POSTER 36

Assessment of Inattention and Executive Dysfunction in Early Huntington's Disease: The Atomoxetine Pilot Trial. L.J. Beglinger, W.H. Adams, H. Paulson, K. Duff, J.G. Fiedorowicz, J.M. Hanson, N. Ramza, D.R. Langbehn, and J.S. Paulsen. *University of Iowa, USA.*

Background: Cognitive symptoms are highly associated with functional disability in Huntington's disease (HD), yet few controlled clinical trials in HD have examined treatments aimed at improving cognition. Such trials have the potential to identify medications that could improve patients' level of independence and quality of life.

Methods: Non-clinically depressed subjects ($n = 20$) with mild HD who complain of inattention will be given either atomoxetine or placebo in a 10-week, double-blind, cross-over study. A battery of standard and computerized neuropsychological tests and measures of psychiatric, functional, and motor symptoms is administered.

Results: To date, 13 participants (69% female; M age 45.2 [11.6] years; M education 13.8 [1.3] years) have completed a baseline assessment and were used in this analysis. The average UHDRS Total Motor Score was 29.0 (15.3), and TFC was 10.5 (2.4). On a self-report measure of inattention (CAARS), 46% reported abnormal symptoms (>1 SD above the normative mean). On a composite cognitive measure of inattention corrected for participants' premorbid intellect, 42% were 1 SD below the mean. On a similar composite for executive functions, 54% reached this threshold. The CAARS did not correlate with either composite score, nor with motor score or TFC. In contrast, the two composite scores correlated moderately with motor score and TFC.

Discussion: This sample has demonstrated both subjective and objective attention and executive deficiencies at baseline that will serve as useful outcome measures to detect drug signal. The utility of self-report measures of cognitive dysfunction in clinical trials requires further investigation. The absence of a relationship between subjective ratings and motor symptoms and TFC might indicate that subjective ratings are tapping a unique aspect of cognitive dysfunction. Alternatively, reduced insight of the participants might necessitate companion ratings. In contrast to the subjective ratings, the objective measures of cognitive dysfunction appear to be strong candidates for endpoints in HD clinical trials.

POSTER 37

A Review of the Use of Concomitant Medication for Huntington's Disease in Europe Between 2004 and 2007 Based on the European HD REGISTRY.

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Much of the focus in Huntington's Disease (HD) research has been on the development of neuroprotective therapies. However, managing HD patients often requires the use of medical treatment aimed at alleviating the symptoms of the disease. Unfortunately, symptomatic medical treatment has made little progress over the last decades. A systematic evaluation of current prescription practices is also missing.

Here, we provide an analysis of the use of concomitant medication for HD based on more than 7,000 entries in the European HD REGISTRY between 2004 and 2007. Among the indications for medical treatment, depression and chorea ranked highest. We compared the use of specific drugs for any given indication across the different European countries. Our results suggest a widespread use of neuroleptics and antidepressants. The preferences for individual compounds varied across Europe, and this variance was not fully explained by the different availabilities of the medications.

We hope that our data will inform the future use of medical treatment in HD and inspire clinical researchers to provide better evidence for the efficacy and tolerability of individual medications. Our data could also be of value for the design of future treatment trials in HD given the propensity of pharmacological compounds to interact.