PROGRAM

Second Annual Huntington Disease Clinical Research Symposium

Organized by the Huntington Study Group

To be held on Saturday, 15 November 2008, in the Pavilion at the TradeWinds Island Hotel, St. Pete Beach, Florida, 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 3.25 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

8:00–9:00 AM
Poster viewing.

9:05–9:45 AM
KEYNOTE ADDRESS—Unmet Clinical Research Needs for Persons with Pre-Manifest Huntington Disease.
Charles Sabine, BA. *NBC News Correspondent, Telbury, Gloucestershire, United Kingdom.*

9:45–10:00 AM
PLATFORM PRESENTATION—Lifestyle Activity and the Age of Onset of Huntington Disease.
K. Trembath,[1] A. Churchyard,[2] Z. Horton,[1] L. Tippett,[3] V. Hogg,[3] R. Roxburgh,[4] D. Velakoulis,[5] V. Collins,[1,6] and M. Delatycki.[1,6]
[1]Bruce Lefroy Centre for Genetic Health Research, Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, Australia, [2]Huntington Service, Calvary Healthcare Bethlehem, Caulfield, Australia, [3]Department of Psychology, The University of Auckland, Auckland, New Zealand, [4]Department of Neurology, Auckland City Hospital, Auckland, New Zealand, [5]Neuropsychiatry Unit, Royal Melbourne Hospital, Parkville, Australia, and [6]Genetic Health Services Victoria, Royal Children's Hospital, Parkville, Australia.

Transgenic HD mouse model studies have shown that raising mice in an enriched environment delays the onset of symptoms, leading us to consider whether pre-morbid lifestyle may affect age-at-onset in humans. Subjects with symptomatic HD were interviewed using a questionnaire to retrospectively ascertain pre-morbid lifestyle, including participation in a range of leisure activities and non-leisure activities (education, occupation, and domestic duties). Recorded activities were classified as physical, intellectual, or passive, and activity scores were generated under the headings leisure, non-leisure, and total lifestyle. Surveys were matched with the subject's age-at-onset and CAG repeat length.

Analysis of age-at-onset data from 154 subjects in Australia and New Zealand showed a mean of 45.7 years (range 21-76), and a strong inverse correlation with CAG repeat length ($r = -0.72$, $p < 0.001$). Furthermore, a relationship between CAG repeat length and average pre-morbid lifestyle passivity was demonstrated ($r = 0.34$, $p < 0.001$), suggesting passivity to be a preclinical manifestation of disease. Upon this background, further analyses were undertaken.

Multiple regression analyses that included CAG repeat length as one predictor variable showed passivity (both in leisure and non-leisure) to be a second, independent predictor of age-at-onset ($b = -0.28$, $p = 0.04$, and $b = -0.27$, $p = 0.02$, respectively), suggesting that a passive lifestyle also contributes to the early onset of symptoms. Leisure activity data covering three life stages (teens, 20s/30s, and 40s/50s) indicate that it is teenage passivity that correlates most strongly with age-at-onset ($r = -0.38$, $p < 0.001$). No relationships of significance were apparent involving age-at-onset and either intellectual or physical activity.

The impact of passivity on age-at-onset is illustrated by comparing the mean age-at-onset in three groups based on lifestyle passivity score. A difference of 4.6 years (95% CI = 1.3 to 7.9) between high and low scoring groups (after adjusting for the impact of CAG repeat length) indicates a significant delay in the onset of symptoms in those who are less passive.

10:00–10:15 AM
PLATFORM PRESENTATION—Longitudinal Structural MRI Data from PREDICT-HD: Striatal and Cortical Changes in Pre-Clinical HD.
E. Aylward,[1] P. Nopoulos,[2] H. Johnson,[2] A. Juhl,[2] V. Magnotta,[2] R. Pierson,[2] D. Langbehn,[2] C. Ross,[3] J. Paulsen,[2] and the PREDICT-HD Investigators of the Huntington Study Group. *[1]University of Washington, Seattle, WA, USA, [2]University of Iowa, Iowa City, IA, USA, and [3]Johns Hopkins University, Baltimore, MD, USA.*

Background: PREDICT-HD is a large multi-site study of individuals with the HD gene expansion who have not yet been diagnosed with the disorder (pre-HD), as well as a smaller group of gene-negative control subjects. Subjects have been followed-up yearly with extensive neuropsychological testing, clinical evaluation, and psychiatric assessment, and every two years with MRI.
Methods: The sample used for the current analysis included 215 pre-HD participants, 35 individuals newly diagnosed with

HD, and 47 age- and sex-matched control subjects. At least two scans, obtained with an interscan interval of 2 years, were analyzed for each subject. Measurements included volumes of caudate, putamen, thalamus, gray, and white matter. Pre-HD subjects were divided into groups based on their estimated proximity to onset (Far, >15 years; Mid, 9-15 years; and Near, <9 years).
Results: Longitudinal change in striatal volume was greater for the Mid, Near, and Diagnosed subjects than for the Control or Far subjects. There was no significant difference between the Far and Control subjects for amount of longitudinal change, and no significant differences among the Mid, Near, and Diagnosed groups. Results for caudate and putamen were the same as those for total striatal volume change. For thalamus, Near and Diagnosed subjects had greater longitudinal change than the other three groups. Effect sizes were calculated, as well as power analyses to demonstrate the number of subjects per treatment group that would be necessary for trials conducted at each preclinical stage. Data for total gray and white volume will also be presented.
Conclusions: Disease-related longitudinal change in striatal volume is observable over a two-year period in individuals who are within 15 years of estimated disease onset, and rate of change is fairly consistent over time once it begins. Observable longitudinal change for the thalamus begins later in the disease process.

10:15–11:30 AM
Break and poster viewing.

11:30 AM–12:10 PM
KEYNOTE ADDRESS—GINA: Public Policy, Private Protection and Implications for Huntington Disease.
Lewis Maltby, JD. *President, National Workrights Institute, Princeton, NJ, USA.*

12:10–12:25 PM
PLATFORM PRESENTATION—Loss of Striatal Dopaminergic Function and Thalamic Compensatory Mechanism During Phenocoversion of Preclinical Huntington's Disease.
K.L. Poston,[1] C. Tang,[1] A. Feigin,[1,2] Y. Ma,[1,2] M. Guttman,[3] J.S. Paulsen,[4] V. Dhawan,[1,2] and D. Eidelberg.[1,2] *[1]Center for Neurosciences, The Feinstein Institute for Medical Research, North Shore-Long Island Jewish Health System, Manhasset, NY, USA, [2]Department of Neurology, North Shore University Hospital and New York University School of Medicine, New York, NY, USA, [3]Department of Neurology, University of Toronto, Toronto, Ontario, Canada, and [4]Department of Neurology, University of Iowa, Iowa City, IA, USA.*

Objective: To examine and validate changes in striatal dopaminergic function and regional brain metabolism during phenocoversion of preclinical Huntington's disease (pHD).
Background: Our recent PET study (Feigin et al., 2007) found progressive declines in striatal D_2-receptor binding in pHD subjects over 44 months, correlating with decreased metabolism in the striatum. During this period, thalamic metabolism was initially elevated above normal and then fell to subnormal levels in the subjects who developed symptoms. To validate these findings, we extended the previous study two years, to 68 months, and now report the preliminary results.
Design/Methods: Twelve presymptomatic HD gene carriers (CAG repeat length: 41.6 ± 1.7; estimated years-to-onset: 10.3 ± 8.6 years) underwent PET scanning with both ^{11}C-raclopride and [^{18}F]fluorodeoxyglucose at baseline, 18, and 44 months. Of these, four subjects were diagnosed with HD during the first 44 months of the study. At 68 months, two symptomatic and two asymptomatic subjects were additionally scanned.
Results: In the four subjects at 68 months, both the caudate and putamen D_2 binding were further decreased relative to values at the first three time points. The decrease in striatal D_2 binding was more pronounced in the two symptomatic subjects than the two pHD subjects, with greater progressive declines in striatal metabolism in the symptomatic subjects. However, thalamic metabolism at 68 months was similar to 44 months, i.e., thalamic metabolism was close to the lower limit of normal in the two symptomatic subjects, but remained above normal in the two pHD subjects.
Conclusion: At the extended 68-month time point, concurrent decreases in striatal D_2 binding and metabolism indicate steady focal loss of striatal projection neurons in pHD. Further, the findings at 68 months support our prior hypothesis that persistently elevated thalamic metabolism is an essential compensatory feature of the preclinical state, with normalization of thalamic metabolism as subjects approach phenoconversion.

12:25–12:40 PM
PLATFORM PRESENTATION—Dimebon in Mild-to-Moderate Huntington's Disease: A Multicenter, Phase 2, Randomized, Placebo-Controlled Trial (DIMOND).
The Huntington Study Group. *University of Rochester Medical Center, Rochester, NY, USA.*

Background: Huntington's disease (HD) is characterized by behavioral and cognitive impairments, in addition to movement disorders. We studied the safety and tolerability of Dimebon (an investigational drug with cognitive benefit in an AD trial) in HD and explored its effects on cognitive and behavioral symptoms.
Methods: Ninety-one subjects with mild-to-moderate HD (TFC ≥5) at 16 centers in the United States and United Kingdom were randomized in a double-blind fashion to Dimebon 20 mg TID (n = 46) or matching placebo (n = 45) for a 90-day treatment period. The primary endpoint was ability to complete 90 days on target dosage of study drug, and secondary measures were UHDRS, ADAS-cog, and MMSE scores.
Results: Dimebon was as well tolerated (87% completion) as placebo (82%) and had a favorable safety profile, with fewer subjects reporting adverse events. The mean MMSE score improved with Dimebon (1 point treatment group difference, nominal $p = 0.03$). There were no other significant differences on UHDRS or ADAS-Cog scales in this short-term study.
Conclusion: Dimebon, 20 mg TID, was safe and well tolerated in HD patients for 90 days and may have a beneficial effect on cognition. Further investigation in HD is warranted.

12:40–1:20 PM
KEYNOTE ADDRESS—The Pathway Forward for Development of New Treatments for Manifest and Premanifest Huntington Disease.
Russell Katz, MD. *Director, Division of Neurology Products, Food and Drug Administration, Rockville, MD, USA.*

POSTER SESSION

Posters will be staffed from 8:00–9:00 AM and 10:15–11:30 AM in the Pavilion.

POSTER 1

Survey of Clinical Trial Interest and Literacy in Huntington Support Groups: Northwest Pilot Project.

L. Veatch Goodman,[1] J. Giuliano,[2] and D. Lovecky.[3] *[1]HD Drug Works, Seattle, WA, USA, [2]CHDI Foundation, Princeton, NJ, USA, and [3]Huntington's Disease Society of America, New York, NY, USA.*

Background: There has been no systematic measure of level of awareness, interest, preferences, or knowledge base regarding clinical research among Huntington families.
Objective: To determine the extent of clinical trial interest and literacy, and to assess response following clinical research education within a cohort of Huntington support group members in the Pacific Northwest.
Methods: Surveys were administered to members of six Huntington support groups before and after a clinical research educational session. Survey questions assessed levels of awareness, interest, clinical trial literacy, and factors influencing participation. All responses were anonymous.
Results: Ninety-nine support group members, including an HD group consisting of symptomatic, gene-positive premanifest, and gene untested (49) and caretakers (50), participated in the survey. Desire for more information was high (80%), as was interest in clinical trial participation (75%), which increased after education (85%). The greatest concerns included drug safety (50%) and time missed from work (30%). Incentives that would increase participation included assistance from a knowledgeable patient advocate (65%), reimbursement travel expenses (45%), and Saturday assessments (40%). Clinical trial literacy was very low in all parameters tested; however, significant learning occurred in concepts relating to criteria, placebo, blinding, patient rights, and consent procedures, but not in understanding of trial phases and medical care during clinical trials.

Though not originally planned as a goal in this project, 7 support group participants were recruited for TRACK-HD.
Conclusions: Similar to survey results in other disease populations, there is low awareness and high interest in clinical trial participation among this Huntington's cohort. Drug safety was the most frequent concern. Assistance from a patient advocate was the most highly rated incentive to increase participation. Though clinical trial literacy is low, it improved significantly after a single educational session. Education in support groups is a mechanism that can increase clinical trial participation.

POSTER 2

The Involvement of Children in COHORT.

K. Quaid[1] and L. Dure.[2] *[1]Indiana University School of Medicine, Indianapolis IN, USA, and [2]The University of Alabama at Birmingham, Birmingham, AL, USA.*

The Cooperative Huntington Observational Research Trial (COHORT) is an observational study designed to collect information in order to learn more about Huntington disease (HD), potential treatments, and to plan future research studies of experimental drugs aimed at postponing the onset or slowing the progression of HD. The study includes both adults and children who have been clinically diagnosed with HD and adults who are part of an HD family. Study visits occur once a year and typically include a neurological examination, family history information, a blood draw for genotyping, and the collection of biological samples for future HD research.

There is increasing interest in enrolling older teenagers (age 15-17 years) who are at risk for HD into COHORT.

In order to gauge interest in this change in protocol, a survey was designed to gather information about attitudes toward this expansion of COHORT on the part of the members of the Huntington Study Group (HSG), many of whom are currently participating in the COHORT study. The survey was posted online, and HSG members were invited to complete the survey. Answers to questions were collected on a five point Likert scale that ranged as follows: Strongly Disagree, Disagree, Neutral, Agree, Strongly Agree.

Respondents were asked whether it was important for affected individuals, unaffected members of HD families, and children to participate in research. They were also asked to imagine that they were members of a family affected with HD and whether they would agree to their own child's participation in an observational trial that included (1) a neurological exam and (2) a blood sample draw for the purposes of DNA analysis for research. Respondents were also asked what their major concerns might be concerning their own or their child's participation. Results of this survey will be presented.

POSTER 3

An Examination of Actual and Potential Discrimination of Individuals at Risk of Huntington's Disease: An Analysis of the RESPOND-HD Data from Australia (Site 144).

A. Goh,[1] O. Yastrubetskaya,[1,2] and E. Chiu.[1,2] *[1]Academic Unit for The Psychiatry of Old Age, The University of Melbourne, Victoria, Australia, and [2]St. Vincent's Aged Psychiatry Service, Melbourne, Victoria, Australia.*

The advent of predictive HD gene testing has raised many unique issues, including the confidentiality of genetic information and the potential for social stigmatization and discrimination. There are also philosophical challenges regarding identity, responsibility, and what it means to live with genetic information that predicts future health status. Some choose not to have predictive testing due to these issues. We examined, as part of RESPOND-HD, the experiences of Australian individuals with a family history of HD and/or who tested for the HD gene in order to evaluate the related social, ethical, and legal issues.

Fifty-four participants so far have completed the RESPOND-HD survey at our Site 144. Information was gathered concerning each participant's background, history, experiences and decision making about genetic testing, family history relating to HD, knowledge of advantages and disadvantages of genetic testing and opinions on testing, and experiences of adverse and unfair treatment. Knowledge about existing laws and policies surrounding genetic discrimination and its use was also gathered. The subscales included questions relating to behavioral, decision-making, and coping style, life experiences, and spiritual, physical, and emotional wellbeing.

There was a wide age range of respondents ($M = 46$ years, $SD = 12$), with 35% male and 65% female participants. All had genetic testing (59% gene-positive, 41% gene-negative). Ninety-eight percent of participants stated that knowing test results was positive and 72% reported 'great benefit' in knowing test results. Many respondents experienced adverse events and felt that they had been treated unfairly. Thirty percent reported specific incidents of genetic discrimination, with complaints in

the insurance arena the most common (18%). Problems with employment, superannuation, and blood donation were also reported. Additionally, there is inadequate knowledge about the existing related laws and policies. Overall, this study revealed significant risk of discrimination to the Australian HD community. Detailed results are being analyzed for presentation.

POSTER 4

The Functional Rating Scale Taskforce for Pre-Huntington's Disease: An Empirically-Driven Initiative for New Scale Development.

K. Evans,[1] K. Anderson,[2] B. Borowsky,[3] K. Duff,[4] J. Giuliano,[3] M. Guttman,[5] A. Ho,[6] D. Langbehn,[4] J. Paulsen,[4] T. Sills,[1] A. Vaccarino,[1] D. Van Kammen,[3] and the FuRST-pHD and PREDICT-HD Investigators and Coordinators of the Huntington Study Group. *[1]Ontario Cancer Biomarker Network, Toronto, Ontario, Canada, [2]University of Maryland, Baltimore, MD, USA, [3]CHDI Foundation, Princeton, NJ, USA, [4]University of Iowa, Iowa City, IA, USA, [5]The Center for Movement Disorders, Markham, Ontario, Canada, and [6]University of Reading, Reading, UK.*

There is an unmet need for the development of treatments for Huntington's disease (HD). The ideal goal would be to develop drugs that can be administered sufficiently early (i.e., pre-HD), such that the full manifestations never develop or are at least delayed. Unfortunately, there is currently no sensitive validated tool capable of measuring symptomatic changes in pre-HD that can be used in clinical trials.

The Functional Rating Scale Taskforce for pre-Huntington Disease (FuRST-pHD) is a multinational, multidisciplinary initiative with the goal to develop a data-driven, comprehensive, psychometrically sound, sensitive, functional rating scale to be utilized in clinical trials to measure symptoms in patients at the pre-HD stage of the disease.

The Taskforce will first identify signs and symptom clusters that should be assessed in pre-HD patients, based on input from a variety of sources, including clinical experts, patients, caregivers, and regulatory agencies. The Taskforce will then develop clinical measures of these signs and symptoms using an iterative processes involving field testing and psychometric analyses. The Taskforce will also rely on the analyses of existing datasets to identify items that may have utility in measuring pre-HD symptomatology. The Taskforce is currently analyzing data from PREDICT-HD, using item response theory (IRT), an approach that has been shown to be a powerful method for evaluating the performance of individual items of rating scales by assessing the relationship between item scores and severity.

The development of a new data-driven, reliable, valid, and easily administered instrument would be valuable in the assessment of pre-HD symptoms in clinical trials. This collaborative effort welcomes input from HD researchers. FuRST-pHD is sponsored by CHDI Foundation.

POSTER 5

An Item Response Analysis of Depressive Symptomatology in Pre-Huntington Disease.

A. Vaccarino,[1] K. Anderson,[2] B. Borowsky,[3] K. Duff,[4] K. Evans,[1] J. Giuliano,[3] M. Guttman,[5] A. Ho,[6] D. Langbehn,[4] J. Paulsen,[4] T. Sills,[1] D. Van Kammen,[3] and the FuRST-pHD and PREDICT-HD Investigators and Coordinators of the Huntington Study Group. *[1]Ontario Cancer Biomarker Network, Toronto, Ontario, Canada, [2]University of Maryland, Baltimore, MD, USA, [3]CHDI Foundation, Princeton, NJ, USA, [4]University of Iowa, Iowa City, IA, USA, [5]The Center for Movement Disorders, Markham, Ontario, Canada, and [6]University of Reading, Reading, UK.*

Historically, the diagnosis of HD has been based on the presence of motor-related symptoms. There is emerging evidence, however, that prior to the manifestation of motor symptoms sufficient to warrant clinical diagnosis, many patients exhibit subtle motor, cognitive, and psychiatric signs, suggesting that people with HD may experience detectable changes before clinical diagnosis (i.e., pre-HD).

There is currently a need for a rating scale that is sensitive enough to detect early symptomatic changes and disease progression in pre-HD. The Functional Rating Scale Taskforce for pre-HD (FuRST-pHD) has been established to develop such a measure. In the initial phase of this program, FuRST-pHD will identify which symptoms should be addressed in a clinical scale, and how best to measure those symptoms.

Depression is thought to be a component of HD that may be present prior to clinical diagnosis. In the present study, FuRST-pHD examined the expression of signs and symptoms associated with depression using data obtained from PREDICT-HD, utilizing a non-parametric item response analysis of depression ratings (UHDRS-III, BDI-II). Item response modeling can be used to evaluate the performance of individual items (or symptoms) on rating scales, assessing the relationship between a score assigned to a particular item and overall severity of the disease.

The results show that pre-HD CAG-expanded subjects ($\geq$37 repeats, n = 752) reported greater depressive symptomatology compared to the comparison group ($<$30 repeats, n = 181). Depression-related symptoms generally increased as a function of overall depressive severity, with six UHDRS-III items (Depressed Mood, Guilt/Self-Esteem, Apathy, Anxiety, Irritability and Anger) and seven BDI items (Sadness, Loss of Pleasure, Guilt, Loss of Energy, Irritability, Concentration, and Fatigue) showing good relation between item score and overall severity. These depression-related signs and symptoms warrant further assessment as items to include on a scale to assess pre-HD symptoms. FuRST-pHD is sponsored by CHDI Foundation.

POSTER 6

Triglyceride-Lowering Effects of EPA in Individuals with Huntington Disease.

R.C. Block,[1] E.R. Dorsey,[2] C.A. Beck,[3] and I. Shoulson[2] for the Huntington Study Group TREND-HD Investigators. *[1]Department of Community and Preventive Medicine and Preventive Cardiology Unit, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA, [2]Department of Neurology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA, and [3]Department of Biostatistics and Computational Biology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA.*

Background: In individuals with Huntington disease (HD), lipid metabolism may be abnormal,[1] and cardiovascular disease is the second most common cause of death. However, treatment of cardiovascular risk factors in those with HD has not received much attention. We therefore examined the lipid lowering effects of an omega-3 fatty acid, the ethyl ester of eicosapentaenoic acid (EPA), in a recently completed HD trial.[2]

Methods: A multicenter, randomized, double-blind, placebo-controlled trial was conducted in North America to determine whether 1 gram twice daily of EPA for 6 months improves motor performance in HD patients. This post-hoc analysis examined the effects of EPA on non-fasting triglyceride and total cholesterol concentrations.

Results: At baseline prior to randomization, triglyceride concentrations in research participants with manifest HD were higher (mean = 171 mg/dL in the EPA arm; mean = 187 mg/dL in the placebo arm) than the National Cholesterol Ed-

ucation Program's goal of <150 mg/dL. In both groups, total cholesterol concentrations (mean = 204 mg/dL in the EPA arm; mean = 208 mg/dL in the placebo arm) were also above the goal of <200 mg/dL. After 6 months of experimental treatment, those randomized to EPA had greater reductions than those randomized to placebo in mean triglyceride concentration (−25.8 mg/dL vs. −11.1 mg/dL; $p = 0.007$) and in mean total cholesterol concentration (−9.5 mg/dL mg/dL vs. −2.5 mg/dL; $p = 0.009$). These lipid lowering effects were not associated with any difference between the groups in the primary motor outcome of the study, the total motor score 4 component of the Unified Huntington's Disease Rating Scale. **Conclusions:** EPA supplementation in individuals with HD was associated with a significant reduction in triglycerides and total cholesterol but not with improved motor function. The long-term sequelae of cardiovascular risk factors in those with HD and the potential to improve prognosis with EPA or other therapies warrant further investigation.

References

1. Valenza M, Rigamonti D, Goffredo D, et al. Dysfunction of the cholesterol biosynthetic pathway in Huntington's disease. J Neurosci 2005;25:9932–9939.
2. Huntington Study Group TREND-HD Investigators. Randomized controlled trial of ethyl-EPA in Huntington disease. Arch Neurol (in press).

Poster 7

Memory for Temporal Sequences for the Early Detection of Cognitive Changes in Preclinical Huntington's Disease.

E. Pirogovsky,[1] B. Bartlett,[2] A. Callazo,[2] J. Goldstein,[3] G. Peavy,[3] M. Jacobson,[4,5] J. Corey-Bloom,[3,5] and P. Gilbert.[1] *[1]SDSU-UCSD Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA, [2]Department of Psychology, UCSD, San Diego, CA,USA, [3]Department of Neurosciences, UCSD, San Diego, CA, USA, [4]Department of Psychiatry, UCSD, San Diego, CA, USA, and [5]Veterans Affairs, San Diego Health Care System, San Diego, CA, USA.*

Previous research implicates the prefrontal cortex in memory for temporal order. Since frontal-striatal circuits are disrupted early in Huntington's disease (HD), temporal order memory may be particularly sensitive to neuropathological changes in preclinical HD. Eighteen presymptomatic gene carriers, 18 age- and sex-matched normal controls, and 18 non-gene–carriers were administered a visuospatial temporal order memory task on a computerized radial eight-arm maze. Presymptomatic gene carriers were assigned to two groups consisting of presymptomatic gene carriers less than five years away from estimated age of onset (HD Close group, n = 10) and presymptomatic gene carriers more than five years away from estimated age of onset (HD Far group, n = 8). On the study phase, the participant was shown a random sequence of circles presented one at a time at the end of each of the eight arms. On the choice phase, the participant was presented with a circle at the end of two of the study phase arms and was asked to choose the circle that occurred earlier in the sequence. Parametric manipulations of the temporal metric were carried out by systematically changing the temporal separation lag between the two circles in the choice phase. As expected, all groups showed superior performance on distal temporal separation lags compared to proximal temporal separation lags. However, the HD Close group demonstrated impairments relative to the HD Far group, non-gene–carriers, and normal controls on more proximal temporal separation lags ($p < 0.05$). There were no significant differences among the HD Far group, non-gene–carriers, and normal controls on the temporal order memory task. These results suggest that temporal order memory deficits are detectable in gene carriers up to five years before HD onset. Temporal order memory may serve as a powerful tool for the early detection of cognitive changes in preclinical stages of this disorder.

Poster 8

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

J. Corey-Bloom,[1,3] J.L. Goldstein,[1] S. Lessig,[1,3] G.M Peavy,[1] and M.W. Jacobson.[2,3] *[1]Department of Neurosciences, UCSD, San Diego, CA,USA, [2]Department of Psychiatry, UCSD, San Diego, CA, USA, and [3]Veterans Affairs, San Diego Health Care System, San Diego, CA, USA.*

Objective: To compare the utility of two brief cognitive screening instruments in patients with HD.
Background: The most commonly used brief screening instrument for cognitive impairment is the MMSE; however, the Montreal Cognitive Assessment (MoCA) contains the same number of total points as the MMSE, requires about 10 minutes to administer, and may be more sensitive to cognitive changes in patients with HD. Correlation between these brief screening instruments and other cognitive and functional measures in HD is largely unknown.
Methods: The MMSE and MoCA were administered on the same day in counterbalanced order to 73 subjects with HD. Associations between MoCA and MMSE with motor, functional, and other cognitive variables were evaluated by Spearman rank correlations.
Results: Scores on the MoCA (mean = 19.2 ± 5.4, range 2-29) were consistently lower, with greater range, than those on the MMSE (mean = 23.5 ± 4.3, range 8-30) for the HD subjects whose mean age and education were 50.7 and 13.9 years, respectively. Mean motor UHDRS = 38.2 ± 16.4; mean Independence Scale (IS) = 68.4 ± 10.1; and mean Total Functional Capacity (TFC) = 6.4 ± 2.0. MoCA score correlated with UHDRS ($r = -0.47$), IS ($r = 0.58$), and TFC ($r = 0.52$) (all $p < 0.0001$); MMSE score also correlated with UHDRS ($r = -0.42$), IS ($r = 0.53$) and TFC ($r = 0.52$) (all $p < 0.001$). However, MoCA score showed consistently higher correlations with other cognitive measures, including Stroop Interference ($r = 0.75$), Verbal Fluency ($r = 0.72$), and Symbol Digit ($r = 0.63$) ($p < 0.0001$) as compared to the MMSE.
Conclusions: Our results suggest that the MoCA may show increased sensitivity to cognitive deficits and better correlation with other cognitive and functional measures than the MMSE in patients with HD. Larger studies will be needed to confirm and extend these findings.

Poster 9

Corticostriatal Abnormalities in HD: A Combined Magnetic Resonance Spectroscopy and Diffusion Tensor Imaging Study.

K.E. Weaver, T.L. Richards, O. Liang, and E.H. Aylward. *Department of Radiology, University of Washington, School of Medicine, Seattle, WA, USA.*

Several lines of evidence have revealed abnormalities within the cortical afferents that innervate the striatum (i.e., corticostriatal tracts) in Huntington's disease (HD). We combined magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) to investigate whether the HD mutation results in specific impairments in axons, myelin, or both within corticostriatal tracts, and whether such impairments are associated with striatal volumetric declines. In 10 individuals with the HD mutation and 10 matched control individuals, we collected

single voxel proton MR spectra from three regions: (1) the head of the caudate, (2) the white matter (WM) positioned just anterior and inferior to the caudate, and (3) the grey matter (GM) within the frontomarginal gyrus. We examined two measures, the MRS metabolite N-acetyl aspartate, (NAA) and the DTI scalar axial diffusivity, that are associated with axonal tissue viability. Additionally, we investigated the integrity of myelin by concentrating on the MRS metabolite choline (Cho) and DTI scalar radial diffusivity, two signals that increase during active demyelinating states. Parallel to previous findings, mean caudate volumes were significantly smaller in HD individuals. Additionally, HD individuals had significantly increased Cho levels and radial diffusivity values extracted from the WM MRS voxel. However, we found no differences in axonal related measures (NAA levels and axial diffusivity) between the groups. The current results raise the possibility of an active demyelinization process within corticostriatal afferents as part of the neuropathological profile of HD, an effect that may possibly account for decreased caudate volumes.

Poster 10

A Randomized, Controlled Trial of Atomoxetine for Cognitive Dysfunction in Early Huntington's Disease.

L.J. Beglinger,[1] W.H. Adams,[1] H. Paulson,[2] J.G. Fiedorowicz,[1] D.R. Langbehn,[1] K. Duff,[1] A. Leserman,[1] and J.S. Paulsen.[1] *[1]University of Iowa, Iowa City, IA, USA, and [2]University of Michigan, Ann Arbor, MI, USA.*

Background: Cognitive symptoms are highly associated with functional disability in HD, yet few controlled clinical trials have examined treatments aimed at improving cognition, which could improve patients' levels of independence and quality of life.

Methods: Atomoxetine is a norepinephrine reuptake inhibitor approved for the treatment of attention deficit/hyperactivity disorder. Twenty participants with mild HD who complained of inattention were given atomoxetine (80 mg) or placebo in a 10-week, double-blind, crossover study. The primary outcome measures were a self-report of attention and an attention and executive neuropsychological composite score. Secondary outcomes were psychiatric and motor symptoms, which were not expected to change.

Results: Regarding safety and tolerability, the rate of any reported side effects while on atomoxetine was 56% (versus 22% on placebo). The most common side effects were dry mouth (39%), loss of appetite (22%), insomnia (22%), and dizziness (17%). There were no serious adverse events related to atomoxetine. There were statistically significant, mild increases in heart rate and diastolic blood pressure on atomoxetine, consistent with other studies, and these increases did not require medical referral. One participant taking creatine had a mildly elevated creatinine level while on atomoxetine. There were no significant improvements while on atomoxetine compared to placebo on the primary outcomes. However, there was evidence of significant placebo effects. There was a significant improvement in global psychiatric functioning under both treatment conditions. There were no group differences on UHDRS total motor score.

Discussion: There were small but significant improvements in self-reported attention and psychiatric ratings while on atomoxetine, but there was also a significant placebo effect obscuring efficacy results. There were mild but common side effects that are not ideal in HD, such as dizziness and loss of appetite. Although atomoxetine was not effective at improving attention at this dose, its safety and tolerability were similar to other studies.

Poster 11

Motor Symptom–Related Metabolic Network in Huntington's Disease.

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Objective: To describe a brain metabolic network selectively expressed in symptomatic Huntington's disease (HD) gene carriers.

Background: A metabolic network specifically associated with HD motor symptoms may be useful in assessing new therapies. We used PET imaging and network analysis to identify a spatial covariance pattern expressed in newly symptomatic HD patients.

Design/Methods: We utilized serial FDG PET to study 12 presymptomatic HD gene carriers at baseline, 18, and 44 months. Four subjects became symptomatic by 44 months. Additionally, two phenoconverters and two non-phenoconverters were scanned at 68 months. To identify a symptom-related pattern, we conducted network analysis to compare the phenoconverted and non-phenoconverted scans at 44 months. Scans from 12 age-matched healthy controls were included for comparison.

Results: We identified an HD symptom-related metabolic covariance pattern (HDSP), which separated symptomatic and preclinical gene carriers ($p < 0.01$). This pattern was characterized by increased metabolism in the primary motor and premotor cortex associated with ventral thalamic reductions. The early symptomatic patients exhibited elevated HDSP expression at 44 months, which increased further at 68 months. Network activity in the non-phenoconverted subjects remained in the range of healthy controls at both time points. Interestingly, computation of HDSP expression retrospectively in scans acquired at baseline and 18 months revealed that network activity was already elevated ($p < 0.01$) in the preclinical HD subjects who subsequently phenoconverted versus those who did not. Across all subjects and time points, pattern activity correlated with UHDRS motor ratings ($p < 0.02$).

Conclusion: The HDSP network emerged as preclinical HD subjects neared clinical onset; its expression also increased as symptoms progressed. A unique feature of the HDSP is its high sensitivity for the motor symptoms of HD. The correlation of pattern activity with clinical ratings indicates that this network may be particularly useful in assessing the emergence of HD symptoms and their response to therapy.

Poster 12

A Metabolic Network Associated with the Progression of Preclinical Huntington's Disease: Application of the Ordinal Trends Analysis to a Longitudinal PET Study.

C. Tang,[1] A. Feigin,[1,2] K.L. Poston,[1] Y. Ma,[1,2] M. Guttman,[3] J.S. Paulsen,[4] V. Dhawan,[1,2] and D. Eidelberg.[1,2] *[1]Center for Neurosciences, The Feinstein Institute for Medical Research, North Shore-Long Island Jewish Health System, Manhasset, NY, USA, [2]Department of Neurology, North Shore University Hospital and New York University School of Medicine, New York, NY, USA, [3]Department of Neurology, University of Toronto, Toronto, Ontario, Canada, and [4]Department of Neurology, University of Iowa, Iowa City, IA, USA.*

Objective: To characterize longitudinal changes in metabolic network activity during phenoconversion in preclinical Huntington's disease (pHD) patients.
Background: Metabolic changes accompanying phenoconversion in HD are not well understood. The ordinal trends (OrT) model is a novel multivariate voxel-based approach developed to identify and quantify progression-related networks in individual subjects (Habeck et al., 2005). We used serial PET imaging to examine activity of an OrT network during the transition from preclinical to symptomatic HD.
Design/Methods: Twelve pHD gene carriers (CAG repeat length, 41.6 ± 1.7; age, 46.8 ± 11.0 years; estimated years-to-onset, 10.3 ± 8.6 years) underwent FDG PET at baseline, 18, and 44 months. Of these 12, four became symptomatic by 44 months. Four patients (2 phenoconverted and 2 non-phenoconverted) were additionally scanned at 68 months.
Results: Using OrT, we identified a highly significant spatial covariance pattern associated with progression in preclinical HD ($p < 0.0001$). The pattern was characterized by declining metabolism in the caudate, putamen, thalamus, and prefrontal cortex across the first three time points. All but one mutation carrier exhibited monotonically increasing network activity over 44 months. The gene carriers who phenoconverted by 44 months had greater network activity ($p < 0.01$) than those who did not phenoconvert during the same time period. This increasing trend continued in the phenoconverters and non-phenoconverters scanned again at 68 months.
Conclusion: We found that OrT network activity increased in pHD subjects followed up to 68 months. This increasing trend was found in subjects who either did or did not phenoconvert during the follow-up period. However, the phenoconverters exhibited a higher level of network activity than the non-phenoconverters both before and after clinical onset. Thus, the OrT network is likely to be a useful biomarker of progression in preclinical HD, which may improve the prediction of symptom onset in mutation carriers.

Poster 13
Early Diagnosis of Mitochondrial Dysfunction in Huntington's Disease In Vivo.
K.E. Conley, S. Jubrias, C. Amara, E. Shankland, D.J. Marcinek, and E. Aylward. *University of Washington Medical Center, Seattle, WA, USA.*

Mitochondria are central to normal cell function, and their dysfunction underlies a wide variety of diseases, such as diabetes (insulin resistance), aging, and both cardiovascular and neurodegenerative diseases. Herein we show new approaches and results that help to identify the mitochondrial changes unique to Huntington's disease that occur well before the onset of symptoms. New optical and magnetic resonance spectroscopic techniques provide for non-invasive, in vivo diagnosis of mitochondrial dysfunction in muscle without the need for a surgical biopsy. These methods reveal changes in mitochondria a decade or more prior to the onset of symptoms. We have found a significant decrease in mitochondrial efficiency in presymptomatic subjects (n = 4, mean age 38 years) versus control subjects (n = 11, mean age 38 years). A continued decrease is evident in symptomatic individuals (n = 3, mean age 53 years), but not yet statistically significant relative to the presymptomatic individuals. Accompanying this loss of mitochondrial efficiency is a corresponding increase in the contribution of non-mitochondrial ATP synthesis from 8% to 23% in the HD individuals. Thus, we have found a substantial reorganization of cellular metabolism in subjects presymptomatic for HD, and this reorganization of cellular energetics continues in the symptomatic individuals. These changes are compared to other disease states to identify the biomarkers reflective of mitochondrial changes that are unique to Huntington's disease. For example, the trade-off between mitochondrial inefficiency and increased glycolysis with stable [ATP] are unique to presymptomatic HD. Identification of biomarkers of HD well before the onset of symptoms provides the opportunity to test interventions that may reverse these dysfunctions and forestall irreversible mitochondrial changes. Thus, innovative noninvasive methods provide new insight into the early cellular changes in HD and provide the opportunity for intervention that may stall the onset of symptoms.

Poster 14
Earliest Functional Declines in Huntington's Disease.
J.F. O'Rourke, L.J. Beglinger, C. Wang, D.R. Langbehn, K. Duff, and J.S. Paulsen. *University of Iowa, Iowa City, IA, USA.*

Objective: Declines in functional skills are observed in patients with Huntington's disease (HD) and have both clinical and research implications. However, the specific areas of early decline have not been investigated. We sought to determine which skill domains weaken most frequently in patients prior to formal diagnosis, as well as the clinical correlates of these early declines.
Methods: Using a large cohort of prediagnosed patients (i.e., DCL < 3) seen at 55 Huntington Study Group clinics, we examined early functional losses using the Unified Huntington's Disease Rating Scale Total Functional Capacity (TFC) and Functional Assessment Scale (FAS) scores. We also analyzed separately individuals with a DCL = 0 or 1 and those with a DCL = 2 to determine the scales' sensitivities to patients with no/minimal motor signs.
Results: Occupational decline was the most frequently reported decline, with 30.10% (TFC) and 26.32% (FAS) of patients reporting some loss of ability to engage in their typical work. Inability to manage finances (TFC 21.87%, FAS 17.42%) and inability to drive safely (FAS 16.24%) were other common functional declines. A *minority* of patients with DCL = 0 or 1 reported functional decline (TFC 15.84%, FAS 14.26%); however, a *majority* of those with a DCL = 2 reported functional decline (TFC 77.54%, FAS 71.03%). The most common functional declines showed relationships with motor functioning, cognitive tests, and depression in a multivariate analysis where all 3 factors were considered simultaneously.
Conclusions: Our analysis of the TFC and FAS provides additional clues as to the earliest functional losses in patients at risk for HD. Fruitful areas for expanded assessment of functional status are performance at work, ability to manage finances, and driving changes. Additionally, existing functional measures may have limited utility when detecting changes in patients with no or minimal motor signs.

Poster 15
Predicting Cognitive Decline: Another Method for Stratifying Samples?
K. Duff,[1] L.J. Beglinger,[1] J.C. Stout,[2] J.S. Paulsen,[1] and the PREDICT-HD Investigators of the Huntington Study Group. *[1]University of Iowa, Iowa City, IA, USA, and [2]Monash University, Melbourne, Australia.*

Background: Neuropsychology uses several methods to determine whether meaningful cognitive change has occurred. Standardized regression based (SRB) formulas, which predict follow-up cognition from baseline cognition, are one such

method. The current analyses examined the feasibility of SRBs to predict cognitive decline in PREDICT-HD.
Methods: Using baseline data on two cognitive tests (Symbol Digit Modalities Test [SDMT]; speeded tapping [TAP]) from the non-gene expanded controls from PREDICT-HD, SRB formulas were calculated via multiple regression to predict follow-up performances on those same two cognitive tests. These SRB formulas were then applied to both groups (gene expanded but prediagnosed; controls) to generate "predicted" follow-up scores, which were compared to "observed" (i.e., actual) follow-up scores.
Results: In controls, baseline SDMT and age best predicted follow-up SDMT scores ($R^2 = .59$, $p < 0.001$). When this formula was applied to both groups, 5% of controls had observed follow-up SDMT scores that were significantly worse than their predicted follow-up scores. However, in gene expanded participants, 10% had significantly worse observed than predicted SDMT scores. Closeness to onset in the expanded group led to greater discrepancies between observed and predicted follow-up SDMT scores (6%, 7%, and 20% impaired for far, mid, and near-to-onset, respectively). For the TAP task, baseline scores also significantly predicted follow-up scores in controls ($R^2 = .46$, $p < 0.001$). Only 1% of the controls had observed follow-up TAP scores that significantly differed from their predicted follow-up scores. In contrast, 22% of gene expanded participants had this significant discrepancy, and closeness-to-onset was again related to greater discrepancies (7%, 17%, and 44%, respectively).
Discussion: SRB formulas were able to identify cognitive decline in this sample of pre-HD individuals, with closeness-to-onset being associated with greater discrepancies between observed and predicted follow-up cognitive scores. Although these formulas might have clinical implications, they also could be used to stratify samples for clinical trials by identifying those individuals who are progressing toward an HD diagnosis. Future studies might examine whether SRBs within a group (e.g., within "near") might be more sensitive than between groups (e.g., case vs. control).

Poster 16

Antidepressant Use in PREDICT-HD: Patterns of Use Relevant to "Naturalistic" Drug Studies.

K. Rowe, L. Beglinger, C. Wang, D. Langbehn, K. Duff, and J. Paulsen. *University of Iowa, Iowa City, IA, USA.*

Background: Depression is a common psychiatric manifestation of Huntington's disease (HD), present in a notable subset of people even prior to motor impairment. Recent HD mouse model studies suggest that treatment with selective serotonin reuptake inhibitors (SSRI) may slow disease progression, making antidepressants a logical target for naturalistic study and controlled trials. However, both the rate of SSRI use and potentially confounding factors contributing to such use are unclear. In this study, we evaluated SSRI use in a large sample of prediagnosed individuals with known genetic status.
Methods: Medication logs from 950 PREDICT-HD participants (756 gene expanded, 194 non-expanded) were examined. At enrollment, 28% were taking antidepressants. Of those, 77% were taking SSRIs, the most common antidepressant class. Subsequent analyses focused on SSRI use. Controlling for age and sex, we examined SSRI use in gene expanded versus non-expanded participants. We used mixed-effect logistic regression to examine SSRI use in relation to diagnostic confidence level and research visit number, controlling for age, sex, and research site.
Results: At baseline, slightly more HD-expanded than control participants used SSRIs (14.7% vs. 9.3%, $p = 0.05$). There are statistically significant trends of increasing SSRI use with increasing diagnostic confidence level ($p = 0.001$), punctuated by a notable increase (OR = 1.56) with transition to diagnosis. Regardless of diagnostic confidence, use also increases with number of research visits (OR = 1.14 per visit, $p = 0.002$.)
Conclusions: Undefined factors drive increasing SSRI usage with greater diagnostic confidence and numbers of visits. The diagnostic confidence trend may reflect depression severity and/or propensity toward treatment increasing with progress toward diagnosis. Increased use with longer participation may also reflect this, or treatment propensity related to research/clinical contact, or temporal trends in HD-related SSRI interest. Regardless, these findings reflect complicating confounders in naturalistic study and underline the need for controlled clinical trials in prediagnosed HD.

Poster 17

Lifestyle Activity and the Age of Onset of Huntington Disease.

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Please see Platform Presentation above for abstract body.

LATE-BREAKING RESEARCH

Poster 18

The Effects of Assistive Devices on Gait Measures in Huntington's Disease.

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Introduction: Falls are frequent in individuals with Huntington's disease (HD), due to gait and balance impairments. Falls often occur when turning, or when maneuvering in tight spaces and around obstacles when walking.
Methods: This study examined the effect of 8 different ambulatory assistive devices (ADs, e.g., canes, walkers) on spatiotemporal gait measures as measured with GaitRite in 21 individuals with HD. Subjects also walked in a figure-of-eight around two chairs placed four feet apart.
Results: During gait without an AD, we found high variability in gait parameters (stride time percent coefficient of variation [%CV] = 12.92, swing time %CV = 7.80, and double support

time %CV = 24.61). Preliminary results indicate that a four-wheeled walker (4ww) induced more normal gait parameters (e.g., higher mean velocity and step length and lower support base, percent of gait cycle in double stance, and step variability) compared to a standard walker (Sw) and cane; more pronounced gait deficits occurred with a Sw. During figure-of-eight maneuvers, subjects moved significantly faster ($p < 0.01$) in the no AD condition than with any device, and significantly slower ($p < 0.01$) with the Sw than any other condition. However, subjects had fewer losses of balance, as manifested by stumbles, when utilizing a 4ww compared to other conditions, indicating that gait maneuverability improves with the 4ww in individuals with HD.

Conclusions: Individuals with HD may have difficulty using Sws and canes because the task complexity and demands on balance are greater than with the 4ww. Wheeled walkers produce more efficient gait patterns than no assistive device, canes, or Sws in individuals with HD and may be the best assistive device for fall prevention in individuals with HD. This study also demonstrated that utilizing walking in a figure-of-eight around obstacles is a sensitive test of dynamic balance function.

Poster 19

Basal Ganglia Pathology in Preclinical and Early Symptomatic Huntington's Disease: Diffusion Tensor Imaging, Magnetic Resonance Spectroscopy, and Volumetric Measures—Which Imaging Modality Is More Sensitive?

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Background: Huntington's disease (HD) is an autosomal dominant progressive neurodegenerative disorder characterized by motor, psychiatric, and cognitive dysfunction. One of the main focuses of clinical research now is to define valid and reliable biomarkers of disease onset and progression that can be of use in future treatment trials. Various neuropathological and neuroimaging studies have indicated early involvement of various components of the basal ganglia.

Aim: In this study, we examined the sensitivity of three magnetic resonance techniques in detecting basal ganglia pathology. Diffusion tensor imaging (DTI) is an MRI technique that measures indices of passive water diffusion, which is believed to reflect the tissue fiber density, fiber architecture, and uniformity of nerve fiber direction. Proton MRS (^{1}H-MRS) is a non-invasive technique that allows the detection of brain chemicals that contain hydrogen, such as N-Acetyl-aspartate (NAA), choline-containing compounds (CHO), creatine/phosphocreatine (CRE), glutamine, glutamate, myoinositol (mI), and lactate (LAC). Volumetric measures of caudate and putamen can be obtained from structural MRI scans.

Method: We examined 25 HD gene carriers (13 preclinical and 12 early symptomatic) and 20 matched gene negative controls. The three imaging modalities were performed on each subject using a GE Signa 1.5T scanner during one scan session. Six HD gene carriers and two control subjects were scanned twice, two years apart. Clinical measures were also collected.

Results: The H-MRS revealed increased choline/creatine and myoinositol/creatine ratios in the basal ganglia in the symptomatic group and decreased glutamate+glutamine/creatine ratios in the preclinical group. Preliminary DTI analyses suggest reduced anisotropy, measured as fractional anisotropy in the basal ganglia. More detailed DTI results and volumetric data will be presented at the meeting. The sensitivity, limitations of, and relationship between the three MRI imaging modalities in detecting basal ganglia pathology in HD will be discussed. The combination of all three techniques may provide a more powerful tool to predict aspects of the clinical presentation.

Poster 20

Music, Meditation, and Huntington's Disease.

M. Pugliese, P. Phan, and J. Sanchez-Ramos. *Huntington's Disease Center of Excellence at USF, Tampa, FL, USA.*

This study investigates the effects of ambient music and binaural beat meditation on Huntington's disease (HD) patients. Of particular interest in this study are the effects on chorea. It is known that Huntington's chorea is reduced or even nonexistent during sleep. This study takes advantage of this as well as the often relaxing and sleep-inducing effects of both ambient music and binaural beat meditation. In binaural beat meditation, a low frequency beat is perceived when two tones of slightly different frequencies are played together through headphones, one tone in each ear. It has been shown that this meditation can be used to "entrain" the brain to *theta* and *delta* brainwave states, states associated with light and deep sleep, respectively. With practice, those who meditate can train themselves to reach these levels faster, with less effort, even while retaining consciousness. Although it may be less documented, it is also known that certain music and sounds can be found to be relaxing for people and may also lead to sleep-like states. The stimulus for this experiment consisted of a continuous, 40-minute listening session with an ambient music section followed by binaural beat meditation in an attempt to create a relaxing, near-sleep or sleeping state in the participants. We predict that since chorea tends to go away during sleep, inducing some level of sleep using these non-invasive methods could lead to a decrease in observed chorea. Chorea was monitored and quantified throughout the experiment using a CATSYS accelerometer, which took specific measurements of movement intensity and any resonant frequencies. The UHDRS motor scale was used throughout the experiment to note any changes in observable chorea. The POMS questionnaire was given before and after the session to assess any changes in depression or anxiety.

Poster 21

Insurance Ownership and Genetic Risk.

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Background: Individuals at risk for Huntington disease (HD) face a possibly shortened lifespan, and, as a result, they may want to own more life insurance. However, insurance companies may discriminate against this population, resulting in lower ownership rates.

Methods: We compared rates of life insurance ownership and amount of life insurance owned between 567 individuals at risk for HD in the PHAROS population (a longitudinal, observational study of individuals at risk for HD) and matched controls in the nationally representative Survey of Consumer Finances (SCF). Individuals were matched based on five-year age group, gender, employment status, race, marital status, whether they had children, and education category. If an individual from PHAROS was matched with more than one individual from the SCF, insurance ownership was compared to the average of the matched controls. We compared rates of insurance ownership and amount of ownership with t-tests.
Results: Compared to their matched controls, individuals at risk for HD were 3 percentage points more likely to own life insurance (86.4% vs. 83.4%, $p = 0.04$). However, among those who owned insurance, individuals at risk for HD were 17 percentage points *less* likely to own a policy larger than $250,000 (49% vs. 32%, $p < 0.001$). Differences in overall ownership do not significantly vary by age, employment, or education; however, differences in ownership of large policies are limited to individuals over 40.
Conclusions: Individuals at risk for a genetic disease are slightly more likely to own life insurance than matched controls, although they tend to own smaller policies. The higher overall ownership suggests higher demand for insurance. The smaller size of policies may point to discrimination. However, this could also point to lower income in this population, which we were not able to adjust for in this study.

Poster 22

Cooperative Huntington Observational Research Trial (COHORT): Baseline Mental Health Risks.

Huntington Study Group COHORT Investigators.

Background: COHORT is a prospective observational study enrolling research participants with manifest Huntington disease (HD), pre-manifest HD, 50% risk for HD, and family members with no risk for HD. Major objectives are to provide systematic clinical assessments and associated biological samples for scientific investigation, expedite recruitment for therapeutic trials, and identify emerging clinical risks among COHORT participants.
Methods: We analyzed baseline demographic and clinical data for the four participant groups as of September 16, 2008. We assessed mental health risks by examining UHDRS ratings for the frequency and severity of depressed mood and suicidal thoughts and compared subpopulations with elevated "risk" scores (>2 on depressed mood or >1 on suicidal thoughts).
Results: In COHORT, 1523 participants (pre-manifest, n = 152, 67.1% female; manifest, n = 777, 52.5% female; 50% risk, n = 267, 65.5% female; no risk, n = 327, 52.0 % female) have enrolled at 39 research sites in the United States, Canada, and Australia. Frequency of depressed mood (pre-manifest, 16.8%; manifest, 14.2%; 50% risk, 11.8%; family members with no risk, 8.0%) and suicidal thoughts (pre-manifest, 5.4%; manifest, 3.1%; 50% risk, 1.6%; family members with no risk, 0.6%) were significantly higher in pre-manifest and manifest subpopulations versus those at no risk for HD ($p < 0.01$). Frequency of suicidal thoughts was significantly higher in the pre-manifest subpopulation versus those at 50% risk ($p = 0.03$).
Conclusion: Mental health risks, including elevated depressed mood and suicidal thoughts, are in keeping with the genetic risk of inheriting the HD gene. The predominance of women in the pre-manifest and at-risk subpopulations compared with manifest HD and family members with no risk for HD is consistent with the gender disproportion observed in the PREDICT and PHAROS observational studies.

Poster 23

Characterization of Frontal Lobe Behavioral Syndromes in Huntington's Disease (HD).

L. Oelke, L. Butterfield, C. Cimino, J. Sanchez-Ramos, M. McCall, M. Pugliese, L. Ling, B. Stell, and J. Annis. *University of South Florida, Tampa, FL, USA.*

Frontal lobe changes are a common feature of Huntington's disease (HD). The Frontal Systems Behavior Scale (FrSBe; Grace & Malloy, 2001) is a rating scale that measures behaviors associated with frontal lobe damage. Three behavioral syndromes—apathy, disinhibition, and executive dysfunction—are quantified as subscales. The FrSBe can be used to discriminate patterns of frontal impairment at two different time points (i.e., Before Diagnosis and Current). In the present study, 24 HD patients completed the FrSBe self-report form. Raw scores were converted into z-scores based on previously reported norms (Grace & Malloy, 2001). Paired t-tests were conducted to test for differences in Before Diagnosis and Current self-ratings on all three subscales. Change scores were calculated by subtracting the Before Diagnosis ratings from the Current ratings for each subscale. Paired t-test analyses revealed that ratings were significantly different for all three subscales: apathy ($t = -5.58$, $p < 0.001$), disinhibition ($t = -2.15$, $p < 0.05$), and executive dysfunction ($t = -4.82$, $p < 0.001$). Examination of z-score means revealed increased severity of symptoms in all three domains *after* the diagnosis of HD as compared to *before* diagnosis. The overall magnitude of the change was largest in the domain of apathy (mean z-score change = 2.69), followed by executive dysfunction (mean z-score change = 1.46), and disinhibition (mean z-score change = 0.62). Generally, apathy, executive dysfunction, and disinhibition ratings before HD diagnosis appear similar to that of a non-clinical sample and fall within normal range. HD patients report elevated rates of apathy, executive dysfunction, and disinhibition symptoms after diagnosis. Overall, behaviors associated with frontal lobe damage appear to be prominent in HD, and these findings suggest that the greatest change, according to patient ratings, may occur within the domain of apathy.

Poster 24

Expert Treatment Preferences for the Motor, Mood, and Behavioral Symptoms of Huntington's Disease.

L. Veatch Goodman,[1] J. Cha,[2] and P. Como.[3] *[1]HD Drug Works, Seattle, WA, USA, [2]Massachusetts General Hospital, Boston, MA, USA, and [3]University of Rochester, Rochester, NY, USA.*

Objective: To determine treatment preferences for Huntington disease symptoms among a small group of objectively chosen Huntington Study Group expert physicians from North America. This study is a follow-up to 2007 survey information obtained from a broader cohort of HSG clinicians.
Background: Though many drugs are available for the treatment of Huntington symptoms, there are inadequate data from controlled studies to guide physicians in choosing, sequencing, or combining agents. The present study is modeled on the Expert Consensus Guideline Series in Psychiatry, which utilizes similar survey information as an aid in the development of suggested treatment guidelines.
Methods: We developed a Web-based survey containing 21 questions and 645 options that included symptoms of chorea, depression, anxiety, irritability, agitation, insomnia, apathy, dystonia, and psychosis. The survey was sent to 30 objectively chosen experts; 21 (70%) responded. Responses were rated on a 3-point scale indicating the appropriateness

of decision making, with choices ranging from first-line (preferred), second-line (alternate), and third-line (usually inappropriate).

Results: Most notably, 90% of respondents did not specify a first choice treatment for the majority of symptoms. This may reflect true lack of preference, or dependence on presence of other symptoms. Majority agreement:

- Preference for of tetrabenazine for chorea (86%) and limiting co-administration of antidepressants only after onset of depression (86%).
- Preference for SSRIs (82%) (Luvox in particular) and inappropriateness for mood stabilizers (>70%) for OCP.
- Lack of consensus on preferred drugs for irritability, agitation, insomnia, and psychosis.

Conclusions: Among this select group, these results show a notable lack of consensus in treatment preference for many Huntington symptoms. This highlights the need, as has been done in other disease communities, to empower a panel of experts who can generate expert guideline suggestions that can guide other clinicians on the appropriate use of drugs in Huntington's.