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Program

Ninth Annual
Huntington Disease
Clinical Research Symposium

Organized by the Huntington Study Group

To be held on Saturday, 24 October, 2015 in the Audubon Ballroom at the Grand Hyatt Tampa Bay in Tampa, FL, USA.

In recognition of the focus on patient-oriented research, the Huntington Study Group (HSG) convened the first annual Clinical Research Symposium in 2007 to present valuable research and information to both clinicians and patients with Huntington disease and their family members. The Symposium consists of poster sessions for visual representation of abstracts and enhanced interaction with authors, as well as presentations from keynote and platform speakers. Time will be allotted for questions and answers after each speaker.

8:00–9:00 AM
Poster Viewing

9:00–9:05 AM
INTRODUCTION—Introduction and acknowledgements by Kevin Biglan, MD, MPH, Chair, HDCRS Program Committee, and Karen Anderson, MD, co-Chair, HDCRS Program Committee.

9:05–9:40 AM
KEYNOTE ADDRESS—Life Hacks: Dealing with Huntington disease.
Erika Bjorklund Pope, Osteopathic Medical Student, *Pacific Northwest University, Yakima, WA, USA.*

Erika Bjorklund knows that there is no easy way to be affected by Huntington disease (HD). The struggles are endless and the sadness can be overwhelming. She has seen the disease affect her father and, now, her older sister. Erika's family refuses to let the disease be a burden but rather something that motivates them to live life to the fullest every day. She spends her time studying to be a neurologist to help other affected families, caring for her sister, and has encountered many motivating stories and "hacks" to make life easier for those suffering from HD. Join Erika Bjorklund as she shares her story and talks about her strategies for staying positive while dealing with HD in her personal and professional life.

9:40–9:55 AM
PLATFORM PRESENTATION—Genetically Engineered Mesenchymal Stem Cells as a Proposed Therapeutic for Huntington disease.
Kyle Fink, PhD. *University of California, Davis, Sacramento, CA, USA.*
K. Pollock[1], H. Stewart[1], H. Nelson[1], K. D. Fink[1], W. Cary[1], K. Hendrix[1], A. Torrest[1], P. Deng[1], J. Gutierrez[1], C. Nacey[1], K. Pepper[1], W. Gruenloh[1], G. Bauer[1], G. Annett[1], T. Tempkin[2], V. Wheelock[2], and J. A. Nolta[1].
[1]Stem Cell Program and Institute for Regenerative Cures, University of California Davis Health System, Sacramento, CA, USA and [2]Department of Neurology, University of California Davis Health System, Sacramento, CA, USA.

We are developing a novel therapy for Huntington disease (HD): implantation of human mesenchymal stem/stromal cells (MSCs) engineered to secrete brain-derived neurotrophic factor (MSC/BDNF). BDNF levels are reduced in the brains of patients with HD. BDNF has been shown in numerous transgenic HD mouse studies to prevent cell death and to stimulate the growth and migration of new neurons, and is thus a lead candidate for neuroprotection in HD. We are conducting detailed tests of MSC/BDNF in HD mouse models in preparation for a proposed Phase I clinical trial of MSC/BDNF implantation into the brain of patients with HD (HD-CELL), with the goal of slowing disease progression.Human MSC/BDNF are manufactured in our UC Davis Good Manufacturing Practices (GMP) Facility. We have shown that MSC/BDNF produces high levels of BDNF and that a multiplicity of infection of 10 virus particles per cell generates a single intact integrant per cell, on average. Our pivotal efficacy studies use both the YAC 128 and R6/2 (CAG 120) transgenic mice to evaluate MSC/BDNF. In the YAC128 model we have successfully demonstrated that implantation of MSC/BDNF resulted in decreased anxiety, as measured in the open field and less severe striatal atrophy when compared with controls. In the R6/2 model we have demonstrated that MSC/BDNF causes increased neurogenesis in the subventricular zone and increases the mean lifespan. Our progress to date supports the completion of our final preclinical studies and our plan to go forward toward regulatory approval. There are potential applications of our research beyond HD. Our biological delivery system for BDNF sets the precedent for adult stem cell therapy in the brain and could potentially be modified for other neurodegenerative disorders such as amyotrophic lateral sclerosis, spinocerebellar ataxia, Alzheimer disease, and some forms of Parkinson disease. It also provides a platform for future gene editing studies.

9:55–10:10 AM

PLATFORM PRESENTATION— Genetic Modifiers of Huntington Disease.

Jong-Min Lee, PhD. *Massachusetts General Hospital, Boston, MA, USA.*

Group 1: J.-M. Lee[1,2*], V. C. Wheeler[1,2*], M. Chao[1,2], J P. G. Vonsattel[3], R. Mouro Pinto[1,2], K. Abu Elneel[1], E. M. Ramos[1], J. Srinidhi Mysore[1], T. Gillis[1], M. E. MacDonald[1,2,5*] and J. F. Gusella[1,4,5*]; Group 2: D. Harold[6*], T. Stone[6], V. Escott-Price[6], Jun Han[6], Alexey Vedernikov[6], P. Holmans[6*] and L. Jones[6*]; Group 3: S. Kwak[7*] and M. Mahmoudi[7]; Group 4: M. Orth[8*] and G. B. Landwehrmeyer[8] on behalf of the European Huntington's Disease Network (EHDN) Registry investigators, J. S. Paulsen[9] on behalf of the Huntington Study Group (HSG) PREDICTHD investigators, E. R. Dorsey[10] and I. Shoulson[11] on behalf of the HSG COHORT, PHAROS and TREND-HD investigators^, and R. H. Myers[12*] on behalf of the HD-MAPS investigators.

[1]Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA, [2]Department of Neurology, Harvard Medical School, Boston, MA, USA, [3]Department of Pathology and Cell Biology and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, New York, NY, USA, [4]Department of Genetics, Harvard Medical School, Boston, MA, USA, [5]Medical and Population Genetics Program, the Broad Institute of M.I.T. and Harvard, Cambridge, MA, USA, [6]Medical Research Council (MRC) Centre for Neuropsychiatric Genetics and Genomics, Department of Psychological Medicine and Neurology, School of Medicine, Cardiff University, Cardiff, UK, [7]CHDI Foundation, Princeton, NJ, USA, [8]Department of Neurology, University of Ulm, Ulm, Germany,[9]Department of Psychiatry, University of Iowa, Iowa City, IA, USA, [10]University of Rochester Medical Center, Rochester, NY, USA, [11]Georgetown University, Washington, DC, USA, and [12]Boston University School of Medicine, Boston, MA, USA.

[*] *Founding GeM-HD Group investigators*

The root genetic cause of Huntington disease (HD) is a HTT CAG trinucleotide repeat expansion, whose size is the primary driver of the underlying pathogenic process leading to the onset of clinical diagnosed symptoms. However, the clinical signs of HD, whether neurological, cognitive, or behavioral, are quite variable even in individuals who have the same CAG repeats. This strongly suggests that other factors, including other genetic variation can influence the rate of the disease process. To identify genetic modifiers of the pathogenic process leading to motor onset, we performed a genome-wide association study using the deviation from expected age at onset (observed onset age minus expected onset age based upon CAG length). We identified 2 genome-wide significant loci harboring genetic modifiers of age at onset of motor signs; regions on chromosome 15 and 8. The region on chromosome 15 comprises 2 independent modifier effects, likely due to different effects on the same gene, which are associated with onset 6 years earlier and ~1.4 years later than expected, respectively. The chromosome 8 region is associated with ~1.6 years of earlier onset than expected. We are currently working to identify the functional variant and gene responsible for the modifier effect from many candidates at each chromosomal location. Interestingly, these genetic modifier loci, discovered based on the continuous age at onset phenotype, were also detected by dichotomous analysis of allele frequencies among only those with extreme late or early age at onset, supporting the power of studying individuals who are phenotypic extremes. The discovery of additional modifiers for other features of HD could therefore be greatly facilitated by deep-phenotyping to identify extreme individuals. The discovery of genetic modifiers, and subsequent delineation of underlying mechanisms, will guide the development of therapeutics based upon target processes that are already validated to be disease modifying in patients with HD.

10:10 – 10:45 AM

KEYNOTE ADDRESS— Silencing the HD Gene: Promises, Obstacles, and Solutions.

Juan Sanchez-Ramos, MD, PhD. *University of South Florida, Tampa, FL, USA.*

The discovery in 1993 of the genetic mutation responsible for Huntington disease (HD) triggered a flurry of research to elucidate the cellular and molecular pathogenesis responsible for the illness. The investigations have identified new targets and approaches for intervention and mitigation of disease. The most promising advance has been the application of gene-silencing technology. The discovery of small double-stranded RNA in plants, (used as a molecular defense against RNA viruses), led to their utilization in animal cells as experimental agents to selectively prevent expression of a gene product. Gene-silencing molecules (siRNA) were soon applied to animal models of HD. Administration of siRNA [and more stable nucleic acids known as antisense oligonucleotides (ASO)] to animal models of HD revealed that the disease process could be halted or even reversed by administration of these novel gene-silencing agents. This remarkable finding heralded the long-awaited cure, but there are obstacles to be overcome. The most significant hurdle concerns delivery of the siRNA (or ASO) to the brain. These molecules cannot penetrate the blood–brain barrier because of their size and chemical structure. So the agents must be delivered directly into brain (by neurosurgical approaches) or into the cerebrospinal fluid (CSF). This approach works very well, even in a large monkey brain, but it is not a feasible way to deliver the agent for the duration of the person's life. Even though ASOs may silence the gene for up to 3 months, that would require infusion of the agent into CSF 4 times a year. Another potential hurdle

relates to the selectivity of the gene-silencing molecules. If the siRNA directed against the HD gene also silenced the healthy nonmutated gene or other genes, there could be deleterious consequences. This obstacle, known as "off-target" effects, is being addressed by many researchers. It has been reported that as long as one does not suppress the normal HD gene > 50%, there are no adverse effects. Other researchers have provided an approach that ensures complete selectivity of the siRNA. Perhaps the biggest hurdle is the delivery system which at the moment requires a surgical intervention to deliver the payload directly into brain or CSF. To overcome this obstacle, novel delivery systems are being developed. Roche is working on a "brain shuttle" designed to carry the payload (the ASO) across the blood–brain barrier so the drug could be given by mouth or into the veins. A research team at the University of South Florida has been working on a nanoparticle system that can deliver the ASO from nose to brain with a nasal spray. These nonsurgical approaches would be safe, noninvasive, and could be administered throughout life.

10:45–11:15 AM
Poster Viewing.

11:15–11:40 AM
PANEL— 2CARE/CREST: Lessons Learned from Neuroprotective Trials in HD and Paths Forward to Meaningful Treatments.
Led by **Andrew McGarry, MD,** *Cooper University Hospital, Camden, NJ, USA.*

11:40 AM–12:00 PM
PLATFORM PRESENTATION— First Time Use of SD-809 in Huntington Disease (First-HD) and Alternative for Reducing Chorea in Huntington Disease (ARC-HD): Results from the Switch Cohort.
Claudia Testa, MD, PhD. *Virginia Commonwealth University, Richmond, VA, USA.*

First Time Use of SD-809 in Huntington Disease (First-HD).
The First-HD Investigators and Coordinators of the Huntington Study Group.

Objective: To evaluate the efficacy, safety, and tolerability of SD-809 in treating chorea associated with Huntington disease (HD).
Background: SD-809 is a deuterated form of tetrabenazine, a vesicular monoamine transporter-2 inhibitor used to treat hyperkinetic movement disorders including chorea, tics and tardive dyskinesia. Deuterium can alter metabolism of small-molecule drugs without changing their pharmacology. SD-809 achieves a comparable area under the curve to tetrabenazine, but with approximately half the dose and half the C_{max}.
Methods: This randomized, double-blind, placebo-controlled trial evaluated SD-809 in subjects with chorea. Study drug was titrated to adequate chorea control over 8 weeks, followed by 4-week maintenance and 1-week washout. Total daily dose ranged from 6 to 48 mg. Entry criteria included total maximal chorea (TMC) score –8, Total Functional Capacity score –5, and no undertreated psychiatric illness.
Results: Ninety subjects (45:45) enrolled (44% female, mean age 53.7 years, mean CAGn = 43.9). The TMC score on SD-809 improved by 2.5 points (21 percentage points) over placebo from baseline to maintenance therapy ($p < 0.0001$). Total motor score (TMS) improved by 4.0 points over placebo ($p = 0.002$). Significantly improved secondary endpoints included patient and clinical global impressions of change (each $p = 0.002$) and SF-36 physical functioning scale ($p = 0.03$). The mean SD-809 daily dose at end treatment was ~40 mg. Three subjects terminated early, 1 receiving SD-809. Adverse event (AE) rates were similar for SD-809 and placebo. Common AEs were irritability (SD-809 6.7% vs placebo 13.3%), somnolence (11.1% vs 4.4%), dry mouth (8.9% vs 6.7%) and dizziness (4.4% vs 8.9%). Depression, anxiety, akathisia, and parkinsonism were reported at the same or lower frequency for SD-809 than placebo.
Conclusions: SD-809 effectively reduced chorea in HD, with an impressive safety and tolerability profile with twice-daily dosing. Treatment with SD-809 improved TMS beyond chorea and improved functional and quality of life measures, suggesting effective symptomatic treatment with good tolerability and overall benefit to patients with HD.

Alternative for Reducing Chorea in Huntington Disease (ARC-HD): Results from the Switch Cohort.
The ARC-HD Investigators and Coordinators of the Huntington Study Group.

Objective: To evaluate the safety and efficacy of switching patients from stable doses of tetrabenazine (TBZ) directly to SD-809.
Background: SD-809 is deuterated TBZ, a centrally acting vesicular monoamine transporter-2 inhibitor. Worldwide, TBZ has been used for decades to treat hyperkinetic movement disorders such as chorea, tics, and tardive dyskinesia. Deuterium is a nontoxic, naturally occurring form of hydrogen that when substituted at key positions on a molecule, can alter drug metabolism and pharmacokinetics. In SD-809, the intrinsic pharmacological activity of TBZ is retained, but a longer half-life enables lower doses to be given with a comparable area under the curve (AUC) and lower Cmax. The properties of SD-809 allow for less frequent dosing and reduced interpatient variability with potential to improve the overall safety profile while maintaining or improving chorea control in Huntington disease (HD).

Methods: Thirty-six patients (60% male, mean age 52.4 years) with HD and adequately controlled chorea on stable doses of TBZ for at least 8 weeks were enrolled at 13 sites across the US and Australia. After an overnight switch from TBZ to an AUC-matched dose of SD-809 (about half the mg dose of TBZ), patients returned for evaluation at weeks 1, 4, and 8. Dose adjustment was permitted after week 1. Chorea was measured using the total maximal chorea (TMC) subscore of the Unified Huntington Disease Rating Scale.
Results: The mean (SE) change in TMC was –0.8 (0.4) at week 1 and –0.8 (0.5) at week 4, compared with baseline. The most commonly reported adverse events were somnolence, fall, and nasopharyngitis. In addition, 21 patients reached week 8 and demonstrated an improvement of –1.9 (0.8) points in TMC. The mean TBZ dose at baseline was 41 mg and the mean SD-809 dose at weeks 1 and 4 was 20 mg and 29 mg, respectively. At week 8, the mean SD-809 dose was 33 mg.
Conclusions: Patients with chorea associated with HD can safely and rapidly convert from TBZ to open-label SD-809. There was continued control of chorea with a possibility of improving chorea control based on minimal adverse effects. Switching from a stable medication directly to an AUC-matched dose of a deuterated compound may be accomplished overnight, without an extended titration period or loss of symptom control.

12:00–12:15 PM

PLATFORM PRESENTATION— Anti-SEMA4D Antibody Ameliorates Pathogenic Processes in Central Nervous System, Cognitive Impairment in the YAC128 Mouse Model of Huntington Disease, and is Well-tolerated in Patients.

Maurice Zauderer, PhD. *Vaccinex, Inc., Rochester, NY, USA.*
M. Zauderer[1], E. Klimatcheva[1], T. Fisher[1], C. Reilly[1], L. Winter[1], C. Mallow[1], H. Bussler[1], S. Torno[1], A. Howell[1], M. Scrivens[1], L. Balch[1], W. Wang[1], M. Paris[1], E. Evans[1], A. Southwell[2], M. Hayden[2], J. Leonard[1], and E. Smith[1].[1]*Vaccinex, Inc., Rochester, NY, USA and* [2]*Centre for Molecular Medicine and Therapeutics, University of British Columbia, Vancouver, BC, Canada.*

Semaphorin 4D (SEMA4D) and its high-affinity receptor, Plexin B1 (PLXNB1), are expressed on neural, endothelial, and immune cells. SEMA4D signaling through PLXNB1 modulates glial cell activation, inhibits migration and differentiation of oligodendrocyte precursor cells (OPC), and disrupts central nervous system endothelial tight junctions. Neuroinflammatory/neurodegenerative diseases are characterized by myelin destruction, and neuronal degeneration, and are often associated with compromise to the neurovascular unit. Antibody neutralization of SEMA4D could therefore ameliorate neurodegenerative disease by 1) reducing damage associated with chronic activation of innate glial inflammatory cells, 2) promoting remyelination through survival, migration, and differentiation of oligodendrocyte precursors, and 3) preventing SEMA4D-mediated breakdown of the blood–brain barrier (BBB). We generated a monoclonal antibody that binds with high affinity to rodent, monkey, and human SEMA4D and blocks Sema4D binding to its cognate receptors. In vitro anti-SEMA4D reverses the inhibitory effects of recombinant SEMA4D on OPC survival and differentiation and blocks astrocyte activation. In vivo, anti-SEMA4D significantly attenuates damage in neuroinflammatory and demyelinating disease models by blocking activation of glial cells, enabling migration and differentiation of OPC, and preserving BBB integrity. Strikingly, in the YAC128 murine transgenic model of Huntington disease (HD), antibody blockade of SEMA4D preserves brain volume and prevents some associated behavioral and cognitive deficits (collaboration with Amber Southwell and Michael Hayden). These data suggest that antibody-mediated neutralization of SEMA4D represents a novel therapeutic strategy for neurodegenerative diseases including HD and multiple sclerosis. A humanized anti-SEMA4D antibody (VX15/2503) was found to be well tolerated at the highest dose administered (20 mg/kg) in 2 Phase 1 clinical trials in different indications. A Phase 2 clinical trial of VX15 anti-SEMA4D antibody in patients with prodromal or early stage HD was initiated in July of 2015. The adaptive design will evaluate safety, tolerability, and efficacy of monthly intravenous administration of VX15/2503, as reflected in clinical features of HD, including cognition (HD-CAB) and quantitative motor assessment, as well as changes in volumetric magnetic resonance imaging parameters and positron emission tomography employing 2 ligands that reflect activation of microglia and astrocytes.

12:15 PM

SYMPOSIUM CLOSING REMARKS—Thank you and conclusions from Kevin Biglan, MD, MPH and Karen Anderson, MD.

POSTER SESSION

Posters will be staffed from 8:00–9:00 AM and 10:45–11:15 AM in White Ibis.

Poster 1

Genetically Engineered Mesenchymal Stem Cells as a Proposed Therapeutic for Huntington Disease.

K. Pollock[1], H. Stewart[1], H. Nelson[1], K.D. Fink[1], W. Cary[1], K. Hendrix[1], A. Torrest[1], P. Deng[1], J. Gutierrez[1], C. Nacey[1], K. Pepper[1], W. Gruenloh[1], G. Bauer[1], G. Annett[1], T. Tempkin[2], V. Wheelock[2], and J.A. Nolta[1]. [1]*Stem Cell Program and Institute for Regenerative Cures, University of California Davis Health System, Sacramento, CA, USA; and*

[2]*Department of Neurology, University of California Davis Health System, Sacramento, CA, USA.*

See platform presentation above for abstract body.

Poster 2

PRE-CELL: Preparing for a Future Planned Phase 1 Trial of Genetically Modified Stem Cells Over-expressing Brain-derived Neurotrophic Factor in Patients with Huntington Disease.

V. Wheelock[1], T. Tempkin[1], S. Duffy[1], A. Martin[1], L. Mooney[1], L. Scher[2], S. Farias[1], D. Swadell[1], C. DeCarli[1], J. Brunberg[3], C.-S Li[4], M. Yarborough[5], A. Dayananthan[1], J. Stout[6], S. Hersch[7], E. Aylward[8], K.D. Fink[9], J. Annett[9] and J. Nolta[9]. [1]*Department of Neurology and HDSA Center of Excellence at UC Davis School of Medicine, Sacramento, CA, USA;* [2]*Department of Psychiatry, UC Davis School of Medicine, Sacramento, CA, USA;* [3]*Department of Radiology, UC Davis School of Medicine, Sacramento, CA, USA;* [4]*Department of Biostatistics, UC Davis School of Medicine, Davis, CA USA;* [5]*Bioethics Program, UC Davis School of Medicine, Sacramento, CA, USA;* [6]*Department of Psychology, Monash University, Victoria, Australia;* [7]*Department of Neurology, Massachusetts General Hospital/Harvard University, Boston, MA, USA;* [8]*Department of Radiology, Seattle Children's Hospital, Seattle, WA USA; and* [9]*UC Davis Institute for Regenerative Cures, UC Davis School of Medicine, Sacramento, CA, USA.*

Background: PRE CELL is a lead-in observational study for a future planned Phase I cellular therapy trial in Huntington disease (HD). The primary objective is to enroll a cohort of up to 40 patients with early-stage HD, in order to characterize the rate of change in clinical, neuroimaging, laboratory, and biomarker correlates of disease progression over a 12–18-month period.

Methods: A linear mixed effects model was used to analyze the repeated measures of the following selected clinical outcome measures in the cohort.

Results: Forty-two patients have been screened and 32 enrolled [38% females, 62% males, mean age 52 years (range 23–74 years), primarily white (91%) with 3 Hispanics (9%)]. Mean expanded allele CAG repeats length is 44 (range 38–59). The estimated change rates for the clinical measures include total functional capacity score –0.9908/year (p = 0.0013); independence score –5.9396/year (p = 0.0039); total motor score 7.843/year (p < 0.0001); change rate in square root of total problem behaviors assessment score –0.17894/year (p = 0.6611), Montreal cognitive assessment score 0.6544/year (p = 0.553). Cognitive assessment scores for the cohort are consistent with those of cohorts identified as early diagnosis in previous studies (Track-HD and CAB-Beta). Preliminary analysis indicates a strong linear relationship between serum mutant Htt and cerebrospinal fluid mutant Huntingtin protein levels (correlation 0.87774, p <0.0001). Analysis of imaging data shows significant reduction in striatal volume over 6 months (data to be presented).

Conclusions: The PRE-CELL study has successfully enrolled a cohort of subjects with early-stage HD and has characterized the rate of change in clinical, imaging, and biomarker measures. These data will be used as a baseline for comparison in patients who may enroll in the future planned Phase 1 trial once regulatory approval has been obtained.

Support for this project was provided by California Institute for Regenerative Medicine (CIRM) grant no. DR2-05415 (Wheelock/Nolta).

Poster 3

First-In-Human Stem Cell Trials in Huntington Disease: A Bioethics Survey.

A. Duffy[1], A. Martin[1], M. Yarborough[1], M. O'Keefe[2], M. Michie[1], D. Swadell[1], and V. Wheelock[1]. [1]*University of California Davis Health System, Sacramento, CA, USA; and* [2]*University of California San Francisco Institute for Health and Aging, San Francisco, CA, USA.*

Background and Objectives: Experimental treatment approaches and first-in-human Phase 1 trials are ethically complex. These studies create challenges for informed consent, impose burdens and risks to patients, and may offer little or no prospect of clinical benefit. Similarly, these studies create bioethical concerns for investigators, coordinators, and study staff. These issues are understudied in the field of regenerative medicine generally and in the Huntington disease (HD) population specifically.

Methods: An anonymous survey of patients with HD and family members regarding attitudes and concerns about participation in a study that involved stem cells, gene therapy, and neurosurgical implantation was approved by the institutional review board at University of California Davis offered on the Huntington's Disease Society of America website from September to December 2014.

Results and Discussion: There were a total of 268 respondents from two groups: 1) individuals at risk for or diagnosed with HD; or 2) family members including spouses, partners, and/or caregivers. Respondents were 96% white, and 69% female [mean age 52 years (range 18–79 years)] and drawn from throughout the USA. Regarding participation in a first-in-human trial, 67% of individuals with or at risk for HD responded positively compared with 92% in family members responding to having a loved one participate. Ethical concerns regarding experimental approaches in HD included none, source of cells, safety/risks, and informed consent. Reasons

for volunteering or supporting this type of study included finding a cure or treatment, helping others, hope, HD warrior/purpose, new knowledge/advancing science, helping family, and helping self. Expressed concerns about involvement in such a study were none, adverse effects, death, lack of efficacy, surgery, pain, and burden of participation. Burdens of participation were felt to be access, risks, uncertainty of the unknown, psychological impact, disclosure of gene status, impact on family, and post-trial support. Additional thoughts from respondents included gratitude, support, remarks on urgency, and sharing of personal stories. Further statistical and qualitative analyses of survey responses will be presented.

Poster 4

Metabolic Biomarkers of Huntington Disease.

H. Budworth[1], D.Y. Lee[2], C. McMurray[1], and C. Ross[3]. *[1]Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA, USA; [2]Department of Bio and Fermentation Convergence Technology, Kookmin University, Seoul, Korea; and [3]Johns Hopkins Medicine, Baltimore, MD, USA.*

Biological markers of disease progression, including presymptomatic stages of disease, would be of enormous benefit to patients and medical professionals. Molecular biomarkers present in human blood can be accessed using a minimally invasive test and could provide a sensitive and practical method of monitoring the disease and disease reversal following treatment. Development of treatments for Huntington disease (HD) remains problematic. To determine whether a treatment is effective, sensitive disease progression biomarkers are needed, especially for the premanifest phase. This would allow the evaluation of neuroprotective treatments in preventing or delaying disease manifestation. There are currently no robust biomarkers to reliably predict and monitor the outcome of therapeutic testing, which would speed up the search. New methods are desperately needed. Our aim is to identify a panel of sensitive and definitive metabolic biomarkers to track disease progression and, ultimately, to use these to test the efficacy of potential therapeutics. Using a combination of gene expression of metabolism-related genes and metabolic profiling we are developing a biomarker panel that can be used to monitor HD in patients.

Poster 5

Functional and Neurovascular Changes in Prodromal HD: Potential for Disease Biomarkers.

J. Hua[1,2], P. Unschuld[3,4], R. Margolis[3,5], J. Pekar[1,2], P. van Zijl[1,2], and C.. Ross[3,5,6]. *[1]The Russell H. Morgan Department of Radiology and Radiological Science, Division of MR Research, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [2]F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD, USA; [3]Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [4] Division of Psychiatry Research and Psychogeriatric Medicine, University of Zürich, Switzerland; [5]Department of Neurology, and Program in Cellular and Molecular Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; and [6]Departments of Neuroscience and Pharmacology, Johns Hopkins University School of Medicine, Baltimore, MD, USA.*

Individuals with the Huntington disease (HD) CAG-repeat expansion develop characteristic morphological brain changes many years prior to the onset of manifest HD. Functional, vascular, and metabolic brain changes may also be present, and represent altered neuronal physiology and metabolism. These functional changes may be detectable early, possibly prior to anatomical changes. Early detection of such changes through the development of functional and physiological imaging markers would allow earlier detection of disease, which could influence the timing of treatment.

Functional connectivity alterations: We studied resting-state functional connectivity, i.e., blood oxygen level-dependent functional magnetic resonance imaging signal synchrony between gray matter regions in the cortico-striatal circuit. Compared with control subjects, reduced functional connectivity was observable in prodromal HD patients between the premotor cortex and caudate nucleus, indicating early motor system dysfunction in prodromal HD.

Neurovascular changes: We investigated changes in arteriolar cerebral blood volume (CBVa), an indicator of homeostasis in the most actively regulated microvascular compartment, in the cerebral cortex. We used the inflow-based vascular-space-occupancy (iVASO) magnetic resonance imaging technique with correction for volume loss. Mean CBVa values in cortical gray matter were significantly greater in prodromal HD patients compared wit controls, with a relative change of 38.5% and effect size of 1.48. This effect was greatest in the frontal cortex, with a relative change of 48.9% and effect size of 2.11. Significant correlations were found between CBVa in the frontal cortex and genetic measures including the CAG-age-product score and estimated years to onset of manifest HD. By contrast, in this small group of subjects, no significant brain atrophy was detectable. Taken together, these data indicate that functional and neurovascular changes can be detected early in the course of prodromal HD, possibly prior to detectable anatomic changes. Further longitudinal studies will be desirable in order to validate some of these measures for tracking progression of disease and response to treatment.

Poster 6

Could Natalizumab Provide Benefits in Huntington disease? A Case Report.

G. Lamotte[1,2], K.E. Anderson[3,4], and F. Amjad[2,3]. *[1-Department of Neurology, University Hospital of Caen, Caen,*

France; [2]Department of Neurology, Medstar Georgetown University Hospital, Washington, DC, USA; [3]Huntington Disease Care Education and Research Center, Medstar Georgetown University Hospital, Washington, DC, USA; and [4]Department of Psychiatry, Medstar Georgetown University Hospital, Washington, DC, USA.

Multiple sclerosis (MS) is an inflammatory, neurodegenerative disorder of the central nervous system (CNS). Huntington disease (HD) is an autosomal dominant disorder caused by a CAG repeat expansion in the IT15 gene. The pathogenesis of HD is still unclear and several studies have focused on neuroinflammation. We report the coexistence of MS and HD in 1 patient. Ms. B. is a 61 year-old woman who was first evaluated in the HD clinic in May 2014. She was diagnosed with HD (42 repeats) in 2012 and presented with chorea, gait impairment, dysarthria, depression, and cognitive impairment. She was also diagnosed with relapsing–remitting MS in 1996, which later progressed into secondary MS. She did not tolerate first-line therapies and was switched to natalizumab, which was discontinued in December 2013 owing to JC virus positivity. The Unified Huntington's Disease Rating Scale motor score (UHDRS) was 68 in May 2014 and she reported significant worsening of her HD symptoms since stopping natalizumab. There was no evidence of relapse or progression of the MS and no new lesions or enhancement on brain imaging. Natalizumab was restarted in October 2014 and her HD symptoms significantly improved (UHDRS = 51 in June 2015). Neuroinflammation with microglial activation in HD may be caused by mitochondrial dysfunction or abnormal immune cell migration causing an increase in proinflammatory cytokines in the CNS. However, in contrast to MS, the role of the peripheral adaptive immune system in HD is unknown and thought to be marginal. Natalizumab reduces the transmission of immune cells into the CNS by interfering with the $\alpha 4\beta 1$-integrin receptor molecules on the cell surface. Therefore, we hypothesize that the penetration of peripheral immune cells into the CNS may contribute to microglial activation, neuroinflammation, and, finally, neurodegeneration in HD. Controlled trials are necessary to explore anti-inflammatory strategies for HD treatment.

Poster 7

Rationale and Design for LEGATO-HD Study: A Multinational, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Laquinimod (0.5, 1.0, and 1.5 mg/day) as Treatment in Patients with Huntington Disease.

R. Reilmann[1], S. Tabrizi[2], B. Leavitt[3], J.C. Stout[4], P. Piccini[5], K.E. Anderson[6], A. Feigin[7], M. Hayden[8], M. Grozinski-Wolff[8], E. Eyal[8], and S. Papapetropoulos[8].

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Introduction: Laquinimod, is an orally active, central nervous system penetrant, immunomodulator with disease-modifying potential currently in clinical development for the treatment of HD. In preclinical models of Huntington disease (HD), laquinimod, reduced behavioral symptoms and prevented brain atrophy and neurodegeneration. Likewise, laquinimod has demonstrated potential in human studies by reducing brain atrophy and disability in multiple sclerosis trials. LEGATO-HD is a Phase 2 proof-of-concept study designed to explore laquinimod's potential in slowing HD progression.

Objectives: To assess the efficacy and safety of laquinimod 0.5, 1.0, and 1.5 mg *versus* placebo in a 12-month study in patients with HD. No clinical data on the effects of laquinimod in patients with HD are available; therefore, a wide dose range is being explored.

Methods: Enrolment of 400 patients (100 patients per dose arm, 1:1:1:1 ratio) is planned. The study aims to detect potential beneficial effects in deteriorating clinical signs and symptoms of HD. Based on previous studies, the Unified Huntington's Disease Rating Scale Total Motor Score is a reliable, validated, and sensitive clinical measure and was therefore selected as a primary endpoint for LEGATO-HD. Secondary endpoints include measures of cognitive capacity, global clinical impression, and total functional capacity. Exploratory endpoints include brain atrophy, Q-Motor, physical performance test, HD quality of life, and a variety of addition cognitive, motor, and behavioral measures. Further ancillary studies will investigate laquinimod's effect on microglial activation using positron emission tomography imaging, peripheral inflammatory markers, and neuronal integrity using magnetic resonance spectroscopy analysis.

Conclusion: There is a significant unmet medical need to ameliorate the progressive neurodegeneration that occurs in HD. LEGATO-HD's innovative design utilizes a combination of well-established and exploratory endpoints, soluble biomarkers, and imaging methodologies that is expected to advance our understanding of the role of inflammation and immunomodulation in HD. Enrolment for this study is underway.

Study is sponsored by Teva Branded Pharmaceuticals in collaboration with EHDN and HSG. Previously presented at CHDI 2015 (Abstract #1585) and MDS 2015 (Abstract #550282).

Poster 8

Laquinimod, an Immunomodulator that Reduces Microglial and Astrocytic Inflammation, as Treatment for Huntington Disease.

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In Huntington disease (HD), inflammatory activity of central and peripheral immune cells such as microglia, astrocytes, and monocytes appears early in the disease course. Activation of immune cells and increased cytokine release correlates with the severity of pathology in HD patients. Teva is conducting the LEGATO-HD study, a clinical trial for HD with the immunomodulator laquinimod. When laquinimod was applied to stimulated human microglia cultures, it reduced microglial density, cytokine release, matrix metalloproteinase-9 production, and phosphorylation of specific signaling enzymes associated with production of proinflammatory molecules. Laquinimod pretreatment of a co-culture of microglia and neurons reduced LPS-stimulated neurotoxicity and nitric oxide production. Laquinimod treatment of human astrocyte cultures reduced production of inflammatory mediators, and in co-cultures with neurons and oligodendrocytes, laquinimod reduced astrocyte-induced neuronal and oligodendroglial apoptosis. In addition to neuroinflammation, loss of brain-derived neurotrophic factor (BDNF) gene transcription occurs in HD and is believed to contribute to the degeneration of the striatum. Mutated Huntingtin protein suppresses vesicle transport and thus disturbs the secretion of BDNF. In previous studies, laquinimod was shown to upregulate BDNF secretion. By elevating BDNF levels in central nervous system tissues, laquinimod may slow degeneration of the striatum. Indeed, in a preclinical model of HD, YAC128 mice, magnetic resonance imaging parameters showed that laquinimod preserved caudate putamen and striatal volume. In the posterior corpus callosum, laquinimod increased axonal integrity [as measured by diffusion tensor imaging (DTI)–fractional anisotropy] and reduced myelin changes (DTI-Dr). Additionally, laquinimod reduced behavioral symptoms in YAC 128 mice. These findings suggest laquinimod reduces immune-mediated neurodegeneration and promotes neuroprotection, supporting its ongoing clinical development for treatment of HD.

Poster 9

Anti-SEMA4D Antibody Ameliorates Pathogenic Processes in Central Nervous System, Cognitive Impairment in the YAC128 Mouse Model of Huntington Disease, and is Well-tolerated in Patients.

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See platform presentation above for abstract body.

Poster 10

Modulation of gait speed in prodromal and early manifest Huntington disease.

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Introduction: Slow gait speed is evident in prodromal (pHD) and early manifest (mHD) Huntington disease (HD). While patients with mHD are able to modify gait speed, stride length at different speeds is lower than controls. It is not clear if this impairment is evident in pHD. Moreover, mechanisms underlying stride length–cadence relationship are not known in prodromal HD. We examined 1) modulation of gait speed in pHD and mHD; and 2) characterized the stride length–cadence relationship.

Methods: Participants included 20 patients with pHD (mean age 41.75 years), 19 patients with mHD (mean age 44.00 years), and 20 controls (mean age 42.45 years). In experiment 1 (internally generated speed modulation) subjects were asked to walk at self-selected normal speed (baseline), fast, and slow speed. In experiment 2 (externally cued speed modulation), we asked subjects to walk in time with a metronome at baseline cadence and 110% of baseline cadence. Primary

outcomes were speed, stride length, and cadence. To assess speed modulation, group by condition repeated measures analysis of variance (ANOVA) was conducted. To examine stride length–cadence relationship, linear regression analysis was used. Intercept, slope, and R2 were assessed using one-way ANOVA.

Results: All groups were able to modify gait speed. The intercept of stride length–cadence regression was lower in patients both with pHD and mHD than in controls ($p < 0.05$). With external cues, patients with pHD and mHD adjusted cadence to match a metronome frequency similar to controls. However, the intercept of stride length–cadence regression was lower in mHD ($p < 0.05$), but not pHD ($p > 0.05$), relative to controls.

Discussion: For patients with pHD subjects, stride length modulation was impaired only during internally generated conditions. Our results suggest that impairment in stride length regulation begins before clinical diagnosis, and may be partly compensated by the use of external cues in pHD.

Poster 11

Step Test Evaluation of Performance on Stairs (STEPS): Assessing Ability to Negotiate Stairs in Individuals with Huntington Disease.

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Stair negotiation is a commonly performed complex motor task. Safe stair navigation requires precise coordination of alternating lower limb movements to achieve proper foot placement on each stair, high-level stability control for temporary single-limb balance during limb advancement and to manage the vertical displacement of body mass, and volitional saccades for acquiring visual information about the characteristics of stairs. The movement dysfunction associated with HD contributes to difficulty with stair negotiation and may increase falls. Currently, there is no validated assessment tool to provide clinicians with adequate information to develop treatment plans to improve stair safety. The MEND laboratory has developed a stair assessment tool called the Schroeder Tool for Evaluating Performance on Stairs (STEPS) and has piloted it with 14 clients in our HD clinic to prepare for a validation study. The STEPS items examine foot placement, continuity of ascent and descent, use of handrail, foot clearance, balance, stepping pattern, and time to ascend and descend. Items are rated on a 0–2 scale, with higher scores indicating better performance. The STEPS was easy to use in a clinic setting and feasible for use by clinic therapists. STEPS scores correlated with Tinetti mobility test (TMT) ($r = 0.65$, $p = 0.012$) scores. Correlation of the total score of the ascent portion of the STEPS with falls on stairs approached significance ($r = –0.48$, $p = 0.081$). The time to ascend or descend did not correlate with fall status or TMT scores. The mean score of the 5 fallers was 7.6 ± 4.51 compared with 11.8 ± 4.52 out of a maximum score of 17 for the nonfallers. Ongoing development of a stair assessment tool that is valid in the HD population is important to improving daily function and safety.

Project supported by Robert A. Vaughan Family Fund.

Poster 12

Multimodal Exercise Improves Fitness and Motor Function in People with Huntington Disease: Results from a Randomized, Feasibility Trial.

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Introduction: This study aimed to evaluate the feasibility and outcome of an intensive, combined aerobic and strengthening exercise intervention in people with early to mid-stage Huntington disease (HD).

Methods: This single blind, randomized trial was conducted across 6 European sites. Participants were randomized to exercise or usual care, and were assessed at baseline and follow-up. The intervention was a 12-week, 3 times per week, progressive aerobic and strengthening program (either home- or gym-based), with over half the sessions individually monitored.

Results: In total, 314 adults were assessed for eligibility: 250 did not meet the inclusion criteria, 32 declined to participate, and 32 were recruited and randomized. Three individuals in the intervention group were withdrawn within the first month owing to concomitant medical conditions, resulting in 14 participants in the intervention group and 15 in the control group. There were no related adverse events. The intervention group had statistically significantly better fitness as measured by predicted VO_2 max [difference: 493.3 ml/min, 95% confidence interval (CI) 97.1–887.6]. There was also a statistically significant improvement on the Unified Huntington's Disease Rating Scale modified motor score (intervention arm 2.9 points lower, 95% CI –5.42 to –0.32). Weight was also statistically significantly different between the groups at follow-up (intervention arm 2.25 kg lighter; 95% CI –4.47 to –0.03).

Conclusion: Here we report for the first time data from a 12-week, 3 times per week exercise program, which was supported by delivery options and individualized monitoring.

Crucially, we demonstrate that this short-term intervention is safe, feasible, and leads to significant improvements in fitness and motor function. Larger scale trials incorporating sustained physical activity are now required to elucidate fully the extended clinical potential of exercise as a neuroprotective agent in HD.

Trial Registration: ISRCTN11392629. This study was funded by the Jacques and Gloria Gossweiler Foundation.

Poster 13

MITIGATE-HD: A Trial of Memantine in Huntington Disease.

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Memantine, an *N*-methyl-D-aspartate receptor antagonist, is currently approved for the treatment of Alzheimer disease. We conducted a randomized, double-blind, placebo-controlled trial evaluating the effects of memantine treatment for Huntington disease (HD) in the context of an ongoing longitudinal observational study (TRACK-HD). A total of 18 participants with early HD who had completed all 4 yearly visits for the TRACK-HD study at the Vancouver site were enrolled. Six months following the fourth and final TRACK-HD visit, patients were randomized to either memantine treatment (20 mg/day) or placebo in a 1:1 ratio. The complete TRACK-HD battery was administered to all subjects after 6 months of study drug administration. The effect of memantine was evaluated against placebo, and all outcomes measures compared with the previous observational data from the TRACK-HD study.

The primary outcome measure was putaminal total *N*-acetyl aspartate (tNAA) measured by magnetic resonance spectroscopy (MRS). MRS analysis proved difficult in this patient group, only 4 memantine-treated and 4 placebo group spectra were of sufficient quality for analysis. No significant change was seen in tNAA for memantine compared with placebo treatment; secondary outcome measures also showed no differences. We then examined the effect participating in a blinded treatment trial had on the TRACK-HD endpoints. The mean rate of change during TRACK-HD was compared with the combined MITIGATE-HD data and revealed that several of the TRACK-HD measures may be susceptible to a placebo effect in clinical drug trials. In conclusion, these results do not support the use of memantine in patients with early HD; however, the small number of patients enrolled and the even smaller number of usable MRS spectra acquired preclude definitive statements on the efficacy of memantine in this population. There was a significant "placebo effect" on specific clinical measures examined, which may influence the choice of primary outcome measures in future HD clinical trials.

Poster 14

The Safety and Effectiveness of Aripiprazole for Treating Irritability and Aggression in Huntington Disease: A Double-blind Placebo-controlled Pilot Study.

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Background: While irritability and aggression are well-reported Huntington disease (HD) symptoms with corrosive effects, there are data on treatments. Aripiprazole, an atypical antipsychotic, has published symptom benefit data outside HD; our group noted good but anecdotal success with aripiprazole in HD clinical practice.

Study design: Patients with HD were randomized to aripiprazole or matched placebo for 8 weeks starting on 5 mg a day, with an optional weekly dose titration to a maximum of 20 mg a day. An open label 6-week extension followed. Primary outcome measures were the 10-question caregiver's Irritability Questionnaire (CIRQ); and the clinician-rated United Huntington Disease Rating Scale (UHDRS) items 29 and 30 (Q29 and Q30, respectively). Both rate frequency and severity (CIRQ 0–3, UHDRS 0–4) for each question on irritability and aggressive behaviors. The 21-question subject-reported Irritability Questionnaire (SIRQ) was a secondary outcome. Safety monitoring included depression, akathisia, and motor and functional assessments.

Results: All 7 enrolled subjects completed the study. Decrease in total CIRQ baseline to end of double-blind treatment was as follows: aripiprazole –14, –12, –6, –17; placebo –26, –3, –7. Large changes in 4 questions drove the placebo group outlier. UHDRS Q29/Q30 change: aripiprazole –14, –7, –4, –1; placebo –4, –5, +5; UHDRS per question mean change –1.6 aripiprazole, –0.3 placebo. SIRQ change: aripiprazole –26, –17, –3, –6; placebo +6, –15, –3; average per question change –0.3 aripiprazole, –0.1 placebo. Dose-related somnolence was the most common side effect. Enrollment challenges included discordant views on irritability symptom levels between clinicians and patients, and clinical need to treat severe symptoms immediately.

Conclusions: Aripiprazole may provide benefit for irritability in HD with good safety. A combination of caregiver, clinician, and subject observations can be used to study psychological symptoms of HD. The realities of symptom stigma, visit frequency, and requiring caregiver and subject participation all affected enrollment. We hope lessons learned can positively inform future study designs.

Disclosures: *Aripiprazole and matching placebo were donated by Bristol-Meyers Squibb. Funding was through the Huntington Society of Canada, grant administered by the Huntington Study Group.*

Poster 15

First Time Use of SD-809 in Huntington Disease (First-HD).

The First-HD Investigators and Coordinators of the Huntington Study Group.

See platform presentation above for abstract body.

Poster 16

Alternative for Reducing Chorea in Huntington Disease (ARC-HD): Results from the Switch Cohort.

The ARC-HD Investigators and Coordinators of the Huntington Study Group.

See platform presentation above for abstract body.

Poster 17

2CARE: A Randomized, Double-blind, Placebo-controlled Trial of High-dosage Coenzyme Q10 in Huntington Disease.

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Background: Huntington disease (HD) is a progressive neurodegenerative disease caused by trinucleotide repeat expansion of the IT15 gene, resulting in an abnormal huntingtin protein. Degeneration observed in HD is thought to be secondary to mitochondrial dysfunction and defective energy homeostasis. Therapeutic agents that improve mitochondrial function and reduce oxidative stress, such as coenzyme Q10 (CoQ), are rational candidates for study in HD.
Methods: This was a multicenter, randomized, double-blind, placebo-controlled study designed to test the hypothesis that chronic treatment of patients with early-stage HD with high-dosage CoQ will slow the progressive functional decline of HD. Patients with early-stage HD (n = 609) were enrolled at 48 sites in the USA, Canada, and Australia from 19 March 2008 to 25 June 2012. Eligible patients were randomized to receive either CoQ 2400 mg/day or matching placebo, then followed prospectively for 60 months. The primary outcome variable was the change from baseline to month 60 in TFC score (for patients who survive) combined with time to death (for those who die) analyzed using a joint-rank analysis approach. Secondary outcome measures included other scores derived from the Unified Huntington's Disease Rating Scale.
Results: In total, 98 patients on CoQ and 108 on placebo completed 60 months on assignment (32% and 35%, respectively). At the time of study cessation, 126 patients in the CoQ group and 132 on placebo were active (42% and 43%, respectively). Withdrawals numbered 57 in the CoQ group and 53 in the placebo group. Twenty-two subjects died over the course of the study in the CoQ group, while 13 died in the placebo group; the majority were classified as related to HD by study personnel. Shortly after the modification of the primary analysis to accommodate death as a poor outcome, the Data and Safety Monitoring Board requested an unscheduled interim analysis for futility in May 2014. This revealed a conditional power of < 5% for the primary analysis and the trial was halted in July 2014. No statistically significant differences were seen between treatment groups for the primary outcome measure (TFC) or secondary outcome measures. CoQ was generally safe and tolerable throughout the study.
Conclusion: The current data do not justify use of CoQ as a disease-modifying treatment in HD.

Poster 18

Update on Open-label Extension of Pridopidine 45 mg Twice Daily in Huntington Disease (OPEN-HART): Safety, Tolerability, and Exploratory Efficacy.

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Background: Pridopidine is a dopamine-stabilizing compound that can enhance or counteract nonphysiologic changes in dopaminergic tone. Pridopidine has been evaluated in several Huntington disease (HD) studies, including HART (A Multi-Center, North American, Randomized, Double-Blind, Parallel Group Study Comparing Three Doses of ACR16 Versus Placebo for the Symptomatic Treatment of Huntington Disease). OPEN-HART is the open label extension of the HART study, using 45 mg twice daily dosing to further investigate safety, tolerability, and efficacy.
Methods: After successfully remaining on study drug through the HART study, patients were re-evaluated for eligibility at a baseline visit using similar criteria to HART. Enrolled patients were contacted by telephone at 1 week and seen in person after 1 month for safety review (concomitant medications, adverse events, compliance), and subsequently every 3 months for alternating safety visits (12-lead electrocardiogram, labs, vital signs) or clinic visits (safety visit activities plus Unified Huntington Disease Rating Scale).
Results: Subjects were enrolled from 24 March 2011 to 7 December 2011, with study activities currently ongoing. In total, 111 patients enrolled at baseline, with 83, 58, and 50 patients completing 12-, 24-, and 36-month visits, respectively. Thirty serious adverse events were reported, the most

common being infection (n = 8), trauma/falls (n = 4), seizure (n = 3; 2 patients not related and 1 possibly related) and anxiety/depression (n = 2). Three deaths occurred, with 1 related to HD (inanition) and 2 unrelated (myocardial infarction, endocarditis). No suicide attempts were reported. Minor deterioration was seen in total motor score (TMS), the primary exploratory efficacy variable, at 12, 24, and 36 months compared with baseline.

Discussion: Pridopidine at a daily dose of 45 mg twice daily has been generally well tolerated over 3 years of administration. Little change in the TMS, the primary exploratory efficacy variable, was seen at any time point compared to baseline. An additional double blind, placebo-controlled study is ongoing to clarify its treatment effect in HD.

Poster 19

Mega-analysis of Behavioral, Cognitive, and Motor Events in COHORT, PHAROS, and PREDICT.

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In studies of neurodegenerative diseases where sample sizes from a single study may be insufficient, a key interest is developing models that borrow strength across data from multiple studies. Mega-analysis, or the meta-analysis of individual data, enables pooling and comparing multiple studies to enhance estimation and power of important patient-features and penetrance. A challenge of mega-analysis is accounting for the complex data structure that if ignored, could lead to bias and incorrect inference. To overcome this challenge, we propose a proportional odds model with time-varying coefficients that compares when different behavioral, cognitive, and motor symptoms can occur across multiple Huntington disease (HD) studies. Using classical techniques in statistics, we establish that our model can handle different dependency and missing features in the data. We apply the proposed method to develop prognostic rules for the occurrence of behavioral, motor, and cognitive impairments in 5-year intervals based on 3 HD studies: COHORT, PHAROS, and PREDICT. Although enrollment criteria were independent across these studies, our method indicates that all 3 show similar tendencies. From ages 35 to 70 years, and after accounting for appropriate baseline features, our method suggests that it is more likely that cognitive impairments and behavioral impairments occur before motor impairments. These results suggest that cognitive and behavioral measures could be used as onset diagnostics prior to motor-based measures, but a further sensitivity analysis is needed to confirm these implications.

Poster 20

Observational and Genetic Research on Huntington Disease in Italy.

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Huntington disease (HD) has a prevalence of about 11/100,000 individuals in Italy, with an estimation of about 6500 affected subjects and 30,000 at risk (Squitieri et al., Clin Genet 2015). The LIRH Foundation (Italian League for Huntington and related diseases) and Research Institute CSS (Casa Sollievo della Sofferenza)-Mendel established an agreement to implement clinical, genetic, and translational research on HD, and to improve assistance to patients and families. The LIRH Foundation is contributing to ENROLL-HD and is presently the HD patients' top recruiter site of 2015. By now, about 200 subjects with HD (from premanifest life stage to the most severe stage 5) are followed up at LIRH and CSS-Mendel in Rome. Total motor score varies between 1 and 116 (mean score 47.8 ± 29), CAG repeat expansion is included between 38 and 64 (mean value 44 ± 4.2; moda 42 CAG), Total Functional Capacity Scale score varies between 13 and 0 (mean score 7.0 ± 4.2) and Independence Scale score between 100 and 15 (mean score 69.6 ± 24.6). Genetically, the Italian population is one of the most heterogeneous cohorts in Europe. Single nucleotide polymorphisms analysis shows a significant predominance of some unusual haplogroups with the rare intragenic A2 haplotype in mutated huntingtin, largely predominating in patients of Italian origin compared to most the frequent A1 and A3 haplotypes of other European descends (Kay et al., Mol Ther, in press). It is, therefore, crucial to extend the genetic analysis to people originating from different part of Italy to possibly relate genetic differences with clinical and epidemiological aspects of HD this country.

Poster 21

Trends in Predictive Genetic Testing Before and after the Genetics Information Nondiscriminatory Act: One Center's Experience.

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Objective: To explore trends in use of insurance and aliases for predictive genetic testing before and after the Genetics Information Nondiscriminatory Act (GINA).

Background: Despite the availability of Huntington disease (HD) genetic testing since 1993, < 10% of individuals at risk for HD have undergone predictive genetic testing in the USA. Reasons for the low uptake of genetic testing are unclear, but barriers may include worries about insurance and employment discrimination. The GINA passed in 2008 provides federal protection from genetic discrimination, and has the potential to mitigate some of these concerns for individuals undergoing presymptomatic genetic testing.
Methods: A retrospective chart review of individuals seen for predictive genetic testing at the University of Rochester Huntington's disease family clinic from 2 epochs corresponding to testing cohorts before (1995–2007) and after (2009–2014) GINA were analyzed. Whether individuals used insurance or alias was extracted. Comparisons between the different epochs were analyzed using the χ^2 test. Only individuals with complete data were included in the analysis.
Results: In the "before" cohort, 16/34 (47%) had complete data compared with 61/62 (98%) in the "after" cohort. Use of insurance was less common in the before cohort compared with the after cohort (31% *vs* 39%, $p = 0.55$). In the after cohort there was a trend towards increasing use of insurance over time peaking in 2012 (64%). Use of an alias was more common in the before cohort compared with the after cohort (25% *vs* 15%, $p = 0.33$). In the after cohort, older patients in general were more likely to use an alias, with the exception of those aged ≥ 45 years.
Conclusion: Use of insurance for predictive genetic testing appears to be increasing and use of an alias decreasing in 1 center before and after GINA. This suggests that GINA may be reducing concerns about genetic discrimination and reducing barriers to predictive testing. This analysis is limited by large amounts of missing data and will need to be confirmed. Additional studies using other data sources and exploring the barriers associated with predictive testing are needed.

Poster 22

The Relationship of Trails Making Test B (TMT-B) Performance and Verbatim Patient-reported Outcomes in the REACH2HD Trial: A Responder Analysis.

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The Phase 2 REACH2HD trial examined the safety and benefits of the metals modulator PBT2 on cognitive impairment, the major and untreatable source of disability in early HD. The Trails Making Test B (TMT-B), a validated measure of executive cognitive performance, improved among research participants assigned to PBT2 250 mg/day compared with placebo. The Huntington Disease Patient Reported Outcome of Problem (HD-PROP) captures most bothersome problem verbatim descriptions reported by individual patients. The relationships between TMT-B performance and their HD-PROP responses were analyzed. The TMT-B and HD-PROP were administered to the 109 REACH2HD participants at baseline and week 26 of experimental treatment [randomly assigned to PBT2 250 mg/day ($n = 36$), PBT2 100 mg/day ($n = 38$), or placebo ($n = 35$)]. Verbatim most bothersome HD-PROP problems were categorized independently without knowledge of treatment assignment into seven umbrella terms. A responder analysis compared individually reported umbrella terms for each of the 15 subjects who showed the greatest improvement and worsening in TMT-B performance between baseline and week 26. The mean ± SD 15 greatest TMT-B improvement subjects (–43.7 ± 20.4 s, range 24–105 s faster than baseline) included2 subjects assigned to placebo, 3 to 100 mg/day, and 10 to 250 mg/day. The mean ± SD 15 greatest TMT-B worsening subjects (72.1 ± 25.3 s, range 35–140 s slower than baseline) included 5 subjects assigned to placebo, 6 to 100 mg/day, and 4 to 250 mg/day. No discernible patterns of HD-PROP terms were found comparing the best and worse TMT-B responders. The HD-PROP umbrella terms responder analysis did not explain the PBT2-related improvement in the TMT-B observed in the REACH2HD trial, perhaps reflecting umbrella categorization informativeness, or insensitivity. Other analytic approaches may be useful such as "natural language processing" of responses or utilizing research participant, caregiver, and clinician HD-PROP reports as a qualitative tool to inform clinical global impression of change (CGIc).

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Poster 23

A Feasibility Study of Working Memory Training for Individuals with Huntington Disease.

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Background: Cognitive impairment is common among patients with Huntington disease (HD), with prominent deficits found in working memory (WM). There are no current

treatments to improve quality of life by slowing the onset of cognitive decline/dementia.

Aim: To examine 1) the feasibility of computerized WM training in patients with HD identified as having cognitive dysfunction; and 2) how patient characteristics contribute to adherence.

Methods: Six patients with early-stage HD were recruited (mean ± SD aged 45 ± 6.0 years; 2 females; CAG length range 42–53). A battery to assess cognitive function was completed, and patients were then introduced to a computerized training program (Cogmed) that targets WM and continuously adjusts for difficulty level over 25 sessions. A training coach made weekly phone contact to inquire about attitude towards training, to note any changes in health, and to provide motivational support. Cognitive testing was repeated upon completion of the program, along with an exit interview to further understanding of patient experiences.

Results: Four patients successfully completed training within the 6-week recommended time frame (mean ± SD 36.5 ± 4.0 days); the two nonadherent patients had reported relatively fewer cognitive complaints at baseline. Patients who completed training endorsed average-to-high levels of motivation and trained, on average, for 38.4 ± 5.1 min per session. Performance improved on trained tasks (mean ± SD improvement score 15.5 ± 14.7, range 13–36), with higher levels of improvement associated with higher motivation for training. Two of the 4 patients reported improvements in their everyday attention. Improvement on a nontrained "following instructions" task was observed in 3/4 patients following completion of the program. No adverse symptoms were reported throughout the intervention.

Conclusions: Select patients with HD can tolerate and complete an intensive cognitive rehabilitation program. Further studies are needed to explore the efficacy of this training program.

Poster 24

Phenotype Characterization of HD Intermediate and Reduced Penetrance Alleles in PREDICT-HD.

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Objective: Huntington disease (HD) is a neurodegenerative disease caused by a CAG repeat expansion on chromosome 4. Pathology is associated with the length of the CAG repeat. The purpose of this study was to examine baseline and longitudinal differences in motor, cognitive, behavioral, functional, and imaging outcomes between persons with CAG repeats in 4 ranges: normal (≤26), intermediate (27–35), reduced penetrance (36–39), and full penetrance (≥40).

Methods: We examined longitudinal data from 1379 participants [280 normal, 21 intermediate [IA], 88 reduced penetrance [RP], and 986 full penetrance [FP] allele ranges]. We used linear mixed models to identify differences in baseline and longitudinal outcomes between groups. Three models were tested: 1) no baseline or longitudinal differences; 2) baseline differences but no longitudinal differences; and 3) baseline and longitudinal differences. We applied the Akaike information criterion to determine the best fitting model for each outcome variable.

Results: Model 3 was the best-fitting model for most outcome variables. Differences between normal and the FP group account for the majority of the significant findings. Some differences between the RP and normal groups were significant. While there were baseline and longitudinal trends of worsening performance across increasing CAG repeat length groups, we found no significant differences between normal and IA groups.

Conclusions: Persons in the FP range exhibit changes across several domains in the prodromal stage. The RP group exhibit changes in some domains. We did not find evidence to support changes in the IA group, though our findings are limited by a small IA sample size.

Poster 25

Genetic Modifiers of Huntington Disease.

Group 1: J.-M. Lee[1,*], V.C. Wheeler[1,2*], M. Chao[1,2], J.P.G. Vonsattel[3], R. Mouro Pinto[1,2], K. Abu Elneel[1], E.M. Ramos[1], J. Srinidhi Mysore[1], T. Gillis[1], M.E. MacDonald,[1,2,4*] and J.F. Gusella[1,4,5*]; Group 2: D. Harold[6*], T. Stone[6], V. Escott-Price[6], J. Han[6], A. Vedernikov[6], P. Holmans[6*], and L. Jones[6*]; Group 3: S. Kwak[7*] and M. Mahmoudi[7]; Group 4: M. Orth[8*] and G. B. Landwehrmeyer[8] on behalf of the European Huntington's Disease Network (EHDN) Registry investigators, J.S. Paulsen[9] on behalf of the Huntington Study Group (HSG) PREDICT-HD investigators, E.R. Dorsey[10] and I. Shoulson[11] on behalf of the HSG COHORT, PHAROS, and TREND-HD investigators, and R.H. Myers[12*] on behalf of the HD-MAPS investigators. *[1]Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA; [2]Department of Neurology, Harvard Medical School, Boston, MA, USA; [3]Department of Pathology and Cell Biology and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, New York, NY, USA; [4]Medical and Population Genetics Program, the Broad Institute of M.I.T. and Harvard, Cambridge, MA, USA; [5]Department of Genetics, Harvard Medical School, Boston, MA, USA; [6]Medical Research Council (MRC) Centre for Neuropsychiatric Genetics and Genomics, Department of Psychological Medicine and Neurology, School of Medicine, Cardiff University, Cardiff, UK; [7]CHDI Foundation, Princeton, NJ, USA; [8]Department of Neurology, University of Ulm, Ulm, Germany; [9]Department of Psychiatry, University of Iowa, Iowa City, IA, USA; [10]University of Rochester Medical Center, Rochester, NY, USA; [11]Georgetown University, Washington, DC, USA; and [12]Boston University School of*

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See platform presentation above for abstract body.

Poster 26

Relationship Between Affective and Cognitive Functioning in At-risk and Presymptomatic Huntington Disease Patients.

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Objective: Huntington disease (HD) is a heritable disorder characterized by cognitive, affective, and motor disturbances as a result of disruptions to frontal–subcortical circuits. Specifically, apathy (decreased motivation/interest) and depression have been observed in prodromal patients. Owing to overlapping characteristics, it can be challenging to distinguish between apathy and depression; however, studies suggest that both are associated with different cognitive processes. The purpose of the current study is to investigate if apathy and depression are independently associated with cognitive functioning in at-risk individuals at the time of genetic testing.

Participants and Methods: Sixty at-risk individuals aged 19–65 years were evaluated prior to genetic testing for HD. Individuals completed the Beck Depression Inventory–II (BDI-II), Apathy Evaluation Scale (AES; Self and Informant Report), and the Montreal Cognitive Assessment (MoCA).

Results: Gene-positive individuals reported significantly higher apathy and depression than gene-negative individuals. Regression analyses were performed to investigate whether self-report measures of depression and apathy predicted performance on 4 cognitive domains on the MoCA (i.e., Executive Function, Language, Attention, and Memory). The regression analysis revealed AES-I significantly predicted Executive Function (β = 0-.697, $p < 0.001$). Neither AES nor BDI-II significantly predicted Language. AES-S significantly predicted Attention ($\beta = 0.492$, $p = 0.011$). Finally, BDI-II significantly predicted Memory ($\beta = -0.384$, $p = 0.015$). These relationships remained (significant or trend) when examining only gene positive individuals.

Conclusion: The results revealed that informant-reported apathy was a significant predictor of lower performance on Executive Function tasks, while self-reported apathy was a significant predictor of Attention. However, depression was the only significant predictor of Memory. These results suggest that apathy and depression may be associated with different cognitive functioning and may be found in gene positive individuals.

Poster 27

A Novel Translational Bioassay for Conformers of Mutant Huntingtin.

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Background: Huntington disease (HD) is a neurodegenerative disorder caused by accumulation of mutant (mt) huntingtin (Htt) in the brain. Determining mtHtt levels in biofluids is critical for assessing therapies that lower mtHtt. Detection of monomeric soluble mtHtt in peripheral tissues or biofluids has been achieved using Homogeneous Time Resolved Fluorescence, Meso-Scale Discovery (MSD), the Erenna, and immunoprecipitation-flow cytometry platforms. Measurment of oligomeric mtHtt would complement these assays and enable a more complete understanding of biofluid mtHtt.

Objective: To develop an MSD assay that detects mtHtt oligomers in human cerebrospinal fluid (CSF) and plasma.

Methods: Rabbit monoclonal antibody Rb1-AL55 was made to Htt1-17 and characterized by Western blot and immunohistochemistry. The MSD platform was used with the monoclonal antibody, MW8, which recognizes mtHtt oligomers and aggregates, and with Rb1-AL55 for detection of mtHtt in human brain, CSF, and plasma.

Results: Rb1-AL55 antibody robustly detected mtHtt in HD brain lysates and labeled nuclear aggregates. Htt signal by MSD assay with MW8/Rb1-AL55 was 6-fold higher in HD human and mouse brain lysates than in controls. In CSF and plasma MSD signals for mtHtt varied between individuals but were consistent in samples from the same person taken 6 months apart. MSD signals in CSF and plasma samples from the same patient with HD were highly correlated and were higher in CSF than in plasma.

Conclusions: The MSD platform, using antibodies MW8 and Rb-AL55, can reliably detect a soluble mtHtt conformer/oligomer that is highly correlated in human plasma and CSF, and may be a useful marker for Htt-targeted therapies or for understanding disease heterogeneity.

Poster 28

An Update on Virtual Visits in Huntington Disease.

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Objective: To evaluate the feasibility and benefit of providing specialty care to individuals with Huntington disease (HD) directly in the home using web-based video-conferencing.

Background: Telemedicine can increase access to specialty care for individuals with neurodegenerative conditions and could facilitate clinical care and research.
Methods: Retrospective review of telemedicine visits for HD in 2 telemedicine clinical research studies.
Results: Twenty-one individuals with HD from 10 states enrolled in the 2 studies. Participants' mean age was 54 years, 89% identified as white (n = 18) and 41% were female. The mean MoCA and TFC scores were 23 (n = 17) and 11 (n = 17) respectively. The mean modified Unified Huntington's Disease Rating Scale Total Motor Score (excluding rigidity and retropulsion scores) was 32 (n = 16). A total of 36 visits were completed via telemedicine. Eleven visits were not completed as 7 participants were lost to follow-up prior to conducting any telemedicine visits. Of those with at least 1 telemedicine visit, 83.3% of the telemedicine visits were completed as scheduled (n = 36). The telemedicine visits lasted, on average, 47 min, with the participants spending 74.2% of that time interacting directly with the physician. Lastly, the participants of these studies expressed high satisfaction with their virtual visits and expressed willingness to use virtual visits to participate in research and to receive care.
Conclusion: Telemedicine visits into the home were feasible for evaluating individuals with HD and may allow for decreased time and costs associated with in-person care and facilitate participation in clinical care and research.

Poster 29

Sensor-Based Remote Measurement of the Motor Symptoms.

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Objective: To explore the feasibility of quantitative methods to measure chorea, bradykinesia, and gait remotely in individuals with Huntington disease (HD) using wearable triaxial accelerometers (PAMSys, BioSensics, Cambridge, MA, USA).
Background: Chorea is one of the most disabling motor symptoms associated with HD, but currently there is no way to objectively monitor chorea severity and other HD-associated motor symptoms remotely in the home.
Methods: In this pilot study, individuals with HD and healthy controls wear movement sensors attached to the chest (days 1–7) and ankles and wrists (day 1). On day 1, the motor section of the Unified Huntington's Disease Rating Scale (UHDRS), timed up and go test, and 10-m walking test is video recorded while patients wear PAMSys sensors. This enables task-specific observation of the UHDRS and other tasks that will aid in the development of computer algorithms to interpret data obtained remotely from the sensors. These assessments will also be compared with standardized quantitative motor (Q-motor) assessments, and objective data obtained from an android phone application, including finger tapping speed, gait, and passive motion.
Results: To date, nine individuals with HD (one female, eight male) and five controls (three female, two male) and have participated in the study. The mean total UHDRS motor score was 41.1 (SD 15.0) and the mean total chorea score was 12.9 (SD 6.0) for individuals with HD. All individuals with HD were able to use the sensors to complete the remote in-home monitoring independently or with the assistance of a caregiver.
Conclusions: Preliminary data obtained from PAMSys sensors have provided promising results that will be presented, suggesting that the motor symptoms of HD can indeed be monitored remotely in the home. Such a device would assist in determining the efficacy of HD symptom-targeting therapies in future clinical trials and may inform clinical care.

Poster 30

CAG Repeat Length and Suicidality in Huntington Disease.

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Methodology: A case–control study using the COHORT Study de-identified database was conducted. Responses were collected from 163 participants. Depression, substance abuse history, and use of benzodiazepines were covariates. Responses to the Unified Huntington's Disease Rating Scale behavioral section pertaining to the frequency and severity of suicidal ideation ("feels life is not worth living", "has suicidal thoughts") were analyzed.
Results: The findings indicate CAG repeat length significantly predicts the frequency of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines. The results of the ordinal logistic regression showed significance [$\chi^2(4) = 14.17$, $p = 0.007$], suggesting that CAG length can predict the frequency of suicidal ideation. Despite taking depression, benzodiazepine use, and history of substance abuse into account, there is still a predictive relationship between CAG repeat length and frequency of suicidal ideation. CAG repeat length was a significant predictor of frequency of suicidal ideation ($p = 0.010$), suggesting that as CAG repeat length increased, the likelihood of being in a higher category of frequency of suicidal ideation also tended to increase. In summary, for every CAG length increase, there is a 0.09 increase in suicidal frequency. The results of the

ordinal logistic regression showed significance [$\chi^2(4) = 11.83$, $p = 0.019$], suggesting that CAG repeat length also predicted severity of suicidal ideation. The covariate depression was a significant predictor of severity of suicidal ideation ($p = 0.003$), suggesting that as depression increased, the likelihood of being in a higher category of severity of suicidal ideation also tended to increase. Thus, when the effect of depression was taken into account, there was no significant relationship between CAG repeat length and the severity of suicidal ideation.

Recommendations: The findings from this quantitative analysis supported using CAG length in a clinician's risk factor assessment to determine the frequency of suicidality.

Poster 31

Development of Standard of Practice Guides for Treatment of Agitation, Anxiety, Apathy, Psychosis and Sleep Disorders in Huntington Disease.

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Description: Utilizing the Institute of Medicine model for the development of trustworthy clinical guidelines, experts drawn from the Behavioral Working Groups of the European Network of Huntington Disease (EHDN) and the Huntington Study Group (HSG) began work in 2014 to develop guides for the treatment of 5 symptoms in Huntington disease (HD). Through a stepwise process, statements intended to optimize patient care were developed for domains that include diagnosis, description, prevalence, prevention, and treatment strategies for Agitation, Anxiety, Apathy, Psychosis, and Sleep Disorder symptoms in HD. Statements were subsequently submitted to a large group of international experts in effort to obtain consensus.

Results: In a highly iterative process, a total of 114 statements were developed into 5 surveys and subsequently sent to about 120 Enroll HD site investigators to gather consensus in the first-round Delphi process. Though we could not confirm how many recipients actually received the surveys, a total of 76 respondents answered at least 1 survey, with 71 completing all 5. There were 37 respondents from EHDN and 40 from HSG. Of the initial 114 statements, 99 reached an agreement level of 85% or more, the defined level for consensus. The pattern and level of agreement and disagreement were similar across all 5 symptoms. Consensus was met on 18/22 statements for agitation, 22/24 for anxiety, 15/17 for apathy, 20/22 for psychosis, and 20/25 for seep disorders. The remaining 15 statements not reaching consensus will be reassessed and refined for a planned round 2 of a single Delphi survey in early fall of 2015.

Poster 32

Exploring the Validity of the Short Version of the Problem Behaviours Assessment (PBA-s) for Huntington Disease: A Rasch Analysis.

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Background: The short version of the Problem Behaviours Assessment (PBA-s) is the recommended outcome measure for behavioral symptoms in Huntington disease. Rasch analysis was used to further investigate the measurement limitations of the PBA-s.

Objectives: 1) To assess the psychometric properties of the 11 severity and frequency items within the PBA-s; and 2) to determine the construct validity of the PBA-s as a clinical outcome measure.

Methods: PBA-s data for 517 participants from Enroll-HD were included in the Rasch analysis. Separate analyses were conducted for the severity and frequency items of the PBA-s, using RUMM2030 software. Achieving fit to the model provides supporting evidence that all items contribute to a single underlying latent trait. This property is defined as internal construct validity.

Results: The total PBA-s severity score demonstrated several important limitations, including disordered response categories for all 11 severity items, local dependency, and poor targeting. However, modifying the original 5-point scoring system to a 4-point system resulted in ordered response categories for seven of the severity items and achieved a good overall fit to the Rasch model. For the total PBA-s frequency score, fit to the model was not achieved even after amendments to the scoring system.

Conclusions: This study suggests that with reduction to a 4-point scoring system, the total PBA-s severity score may be considered a valid clinical outcome measure. This study also suggests limitations in the use of a total PBA-s frequency score.

Poster 33

HDQLIFE: A New Measurement System to Evaluate Health-related Quality of Life in Huntington Disease.

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Aims: There is a strong need for new measures that can sensitively and efficiently measure health-related quality of life in Huntington disease (HD). The HDQLIFE study developed a new measurement system using state-of-the-science mixed method approaches. This system includes several carefully calibrated item banks (sets of questions) that can be administered through a computer adaptive test (CAT) framework. CATs, or smart tests, allow for sensitive construct assessment with a minimal number of items (each item that is presented to the participant is based on his/her previous response).

Methods: In total, 539 individuals with prodromal, early-stage, or late-stage HD completed newly developed HD-specific item pools (159 items) examining chorea, speech and swallowing difficulties, and end-of-life concerns. Exploratory and confirmatory factor analyses were utilized to evaluate unidimensionality of this set of items. This was followed by item response theory (IRT) graded response model analysis to estimate parameters of items that met the unidimensional criteria, and differential item functioning to ensure stable psychometric properties across patient characteristics (sex, age, education). Short forms were also created to be used where CAT is not feasible.

Results: Five new measures were developed according to this methodology: Chorea, Speech Difficulties, Swallowing Difficulties, Concern with Death and Dying, and Meaning and Purpose. All measures (except Meaning and Purpose), were developed as CATs and corresponding 6-item short forms. Meaning and Purpose was developed as a 4-item short form. Short forms were selected using clinician input, as well as psychometric properties of items. All measures met unidimensional criteria (as evidenced by exploratory and confirmatory factor analyses); psychometric properties were supported by both IRT and differential item functioning analyses.

Conclusions: HDQLIFE includes HD-specific measures that evaluate Chorea, Difficulties with Speech, Difficulties with Swallowing, Concern with Death and Dying, and Meaning and Purpose. Scores for each of these measures are converted into a T-score with a mean of 50 and SD of 10; higher scores indicate more of the specified construct (i.e., higher scores on Chorea indicate more self-reported chorea). These are the first CATs developed specifically for use in HD. Such measures are potential candidates for inclusion as standard outcomes measures in clinical and interventional trials.

Poster 34

Status Dystonicus Presenting as Status Epilepticus in a Juvenile Huntington Disease Patient.

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Background and Objective: Dystonia is a common feature of Juvenile Huntington disease (JHD), presenting unique management challenges when compared with the adult-onset form of Huntington disease. Here, we present a particularly challenging case that underscores this point.

Method: Case report.

Results: A 16-year-old girl with a history of JHD (CAGn = 82/17) presenting with cognitive difficulties at the age of 6 years, motor impairment at the age of 7 years, focal and generalized seizures starting at the age of 8 years treated with oxcarbazepine and then levetiracetam, limb dystonia by the age of 9 years, and progressive motor impairment leading to loss of ambulation by the age of 15 years was admitted to the pediatrics service with fever due to a buttock wound and recurrent tonic spasms consistent with status epilepticus refractory to antiepileptic drug therapy. Continuous electroencephalography (EEG) monitoring showed a 12-hz background rhythm. Twelve events were captured during monitoring in which there was no electrographic correlate with the spasms, pointing to a diagnosis of status dystonicus. The episodes resolved after treatment with clonazepam and baclofen.

Discussion: Both focal and generalized seizure types are known to occur in JHD. Dystonia is frequently more severe in JHD than in adult-onset HD. Status dystonicus is defined as recurrent or occasionally sustained muscle contractions or spasms that cause abnormal posturing. Common antecedents

may include infection, medication changes or trauma. In this case, the patient was initially diagnosed with status epilepticus. Continuous EEG monitoring and clinical examination showed that the patient's stereotypic movements were, in fact, due to status dystonicus. This case illustrates the complexity of diagnosis and management of patients with JHD, and can serve as evidence that patients with JHD may be best managed at tertiary care centers where more comprehensive resources, such as continuous EEG and movement disorders consultation, are available.

Poster 35

Attitudes Toward Clinical Trials and Genetic Disclosure in Autosomal Dominant Alzheimer Disease: Implications for Huntington Disease.

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Background: Treatments for autosomal dominant neurodegenerative conditions can be tested in patients who have no symptoms but will develop disease. The design of prevention clinical trials in autosomal dominant conditions, however, may be complicated by low rates of genetic testing among persons at risk to inherit disease-causing mutations.

Methods: We anonymously surveyed participants in the Dominantly Inherited Alzheimer's Network to better understand their attitudes toward genetic testing and clinical trials. Participants were asked whether they knew their genetic status, did not know their genetic status but wished to, or did not know and preferred not to know their genetic status. Participants not interested in genetic testing answered whether they would change their mind if learning that they carried a mutation gave them the opportunity to participate in a trial. Regardless of preference toward genetic testing, participants answered questions related to interest in trials and how placebo ratios and open-label extension studies altered that interest.

Results: Eighty participants completed the survey; 40% knew their genetic status, 15% did not know but wished to learn their status, and 45% did not wish to learn their genetic status. Seventy-two percent of participants who did not wish to learn their genetic status reported that they would change their mind in the setting of a clinical trial. Eighty percent of all participants reported that they were interested in participating in a clinical trial. The proportion interested dropped when there was a possibility of a placebo. The higher the chance of a placebo, the lower the interest. Nearly all participants (100% of those who knew or wished to know and 96% of those who did not know but would be willing to learn their genetic status in the setting of a clinical trial) would be interested in a trial with an open label extension.

Conclusions: The anonymous nature of the survey and the inability to determine whether differences exist between responders and nonresponders limit interpretation of these results. Nevertheless, the results support the conduct of trials to prevent autosomal dominant Alzheimer disease. Similar data are needed in Huntington disease and may be instructive toward designing feasible and appropriate prevention clinical trials.

Poster 36

Communication in Huntington Disease: An Empirical Review.

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Communication is a multifaceted discipline that includes language, emotion, speech, and proxemics, as well as social and environmental factors. Communication is particularly relevant in the process of adjusting to chronic illnesses such as Huntington disease (HD), with communicative patterns being significantly related to clinical outcomes. To our knowledge, no existing review has been carried out on the range of empirical studies on communication in HD, nor any clear understanding on which components of communication will benefit from further investigation. An empirical review was conducted to identify the elements of communication that have been investigated with people who had symptomatic HD, and the differing methodological approaches. The PubMed, PsycINFO, and Linguistics and Language Behavior Abstracts databases were searched systematically from January 1993 to January 2015, reference lists of included papers were hand-searched, and 49 studies were identified across four topic areas; communicative skills, emotion, language, and speech. The results illustrate that HD impairs language skills, recognition of negative emotions, and speech production when compared with both healthy participants and other neurodegenerative conditions. Preliminary evidence was also found for the significant impact of social and environmental factors on communicative abilities. Areas identified for future research include emotion expression and other nonverbal components of communication, as well as the effect of both impairments and social factors on the functional communicative capacity of people with symptomatic HD.

Poster 37

Healthcare Delivery in Huntington Disease: An Exploratory Global Survey.

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Background: Little is known about variation in service provision for those affected with Huntington disease (HD). The Care Improvement Committee of the Enroll-HD study did a survey to map how services are organized and delivered across HD clinics and Enroll-HD research sites globally.
Methods: Enroll-HD and other eligible sites (EHDN's REGISTRY sites) were invited to respond to a 69-item survey that was distributed in 2014. Out of 232 sites surveyed, 121 (52.2%) sites in Europe, North America, Latin America, and Australasia responded. Data were analyzed using descriptive statistics.
Results: A majority of centers (61.1%) serve a population of > 1.5 million people, and 86.0% of centers report seeing patients from outside their region. A majority of centers (59.7%) follow 50–199 patients, while 21.9% care for > 200 patients. Most centers (75.2%) provide care in all stages of HD. Most centers (86.8%) are integrated in larger departments that offer consultations to other types of patients. The majority (77.0%) of patients with HD receive care though government-supported/funded programs. The center leader is usually a neurologist (79.5%); other centers are led by a psychiatrist or neuropsychiatrist (9.4%) or a clinical geneticist (5.1%). Multidisciplinary case reviews are offered by 54.6% and outreach visits by 48.2% of centers. Videoconferencing and telemedicine are used by 23.6%. Caregivers are usually (94.8%) seen together with patients, but separate consultations for caregivers are offered in more than half of the centers. Most centers (70.4%) report following published guidelines or local care pathways for HD.
Conclusion: Most centers serve a large population and provide multidisciplinary care. The survey gives insight into factors underpinning HD service delivery. There is a need for more in-depth studies of clinical practice to understand more about variations across centers, high-quality service provision, and multidisciplinary care.

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HD Trialfinder: A Clinical Trial Matching Resource for the North American Huntington Disease Community.

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We have moved into a very promising time for Huntington disease (HD). With each passing day more and more pharmaceutical and biotechnology companies are entering into the HD drug development arena. While this is good news for all those affected by HD, the recruitment of clinical trial participants in a timely manner is the greatest obstacle to developing the next HD treatment. In the past, if individuals were interested in trials, they were directed to resources such as Clinicaltrials.gov. Unfortunately, sites like this are outdated, difficult to understand, and often do not provide a direct connection to the study site coordinator. All of these are unnecessary barriers to trial participation. The Huntington's Disease Society of America (HDSA) identified the lack of a patient friendly, reliable clinical trial resource as a critical need in the HD community so we collaborated with EmergingMed to launch in April 2015 a new resource called HD Trialfinder. The HD Trialfinder, is a free, easy-to-use clinical trial matching service that connects individuals with HD, caregivers, healthy volunteers, and physicians with current HD studies around North America. The HD Trialfinder is updated daily to ensure its database includes only those interventional and observational HD studies that are currently recruiting in the US and Canada. The trial listings in the HD Trialfinder come from publicly available sources, such as Clinicaltrials.gov. In addition, HDSA makes direct outreach to researchers and trial sites across the country to include their HD-related clinical research studies that may are not listed in Clinicaltrials.gov. Trials not listed in ClinicalTrials.gov are subject to additional review by the HDSA Scientific Advisory Board prior to being listed on the HD Trialfinder to ensure that listings only include credible trials and investigators. For example, HDSA requires scientists involved in the HD Human Biology Project to have their exploratory clinical studies posted in HD Trialfinder. The HD Trialfinder only lists trials and studies that have institutional review board approval. To access HD Trialfinder, go to www.hdsa.org or www.HDTrialfinder.org. First-time visitors must create an account by providing an email address, and first name or alias. In the first 3 months, HD Trialfinder had 700 users. The program will then allow you to create unlimited profiles for yourself, family, friends, or your patients. To best match to a trial you must complete a brief questionnaire composed of 11 questions about yourself (or the individual affected by HD). HD Trialfinder will provide you with a patient-friendly summary of the different clinical studies, as well as the contact information for the nearest HD study coordinator to start the conversation about your eligibility. In summary, all HD organizations and families share a common goal of finding effective therapies for HD as quickly as possible. In partnership with other HD organizations that have agreed to assist HDSA increase the promotion of this resource, it is our hope that HD Trialfinder will work to expedite the recruitment of current and future HD trials and help make effective therapies for HD a reality.

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Supporting Youth Affected by HD: Preliminary Results from the North American Youth Summer Camp Evaluation.

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Camp overview: The North American Huntington Disease (HD) Youth Summer Camp was designed to provide young people aged 15–23 years a break from home life and an opportunity to gain peer and professional support around HD issues and HD education. Through a mix of activities and educational sessions, the camp offers young people the opportunity to build coping skills, peer relations, support, and HD education. Campers must have a parent/family member with HD, live in the US or Canada, and complete application. A total of 55 applications were received and all offered admission. Forty-five campers accepted. All sexes, races, and ethnicities were eligible to attend the camp.

Camp evaluation: An evaluation component was added to assess the impact of the camp and provide data for future camp development. The evaluation consists of a survey administered at 4 time points, including a precamp survey, assessing differences in self-esteem, social support, resilience, health-related quality of life, and HD issues.

Precamp survey results: At total of 35 campers completed the precamp survey [23 female, 12 male; mean age 18 years (range 14–23 years)]. Campers were predominately white ($n = 33$) and from the US ($n = 29$). Campers describe isolation from friends ($n = 24$), felling less "normal" than other children ($n = 22$), having not enough information about testing ($n = 25$), or relationships and HD ($n = 13$). Only 4 had any contact with an HD organization (Huntington's Disease Youth Organization, Huntington's Disease Society of America, or Huntington Society of Canada). Campers scored low on both self-esteem ($n = 11, < 15$) and resiliency measures (M = 2.98)

Implications: Findings from the precamp survey suggest youth affected by HD are an isolated group, in need of not only HD specific information, but also support around issues of self-esteem and well-being. These results highlight the stated goals of the camp, to provide support and education, while underscoring the need for the provision of HD youth focused programming.