HSG 2022
ANNUAL MEETING

TAMPA, FLORIDA

Abstracts of the 29th Annual Meeting of the Huntington Study Group

November 3-5, 2022

Manuscript Editor
Joy Drohan

HSG Publications Committee
Erin Furr Stimming, Eric Molho, Clement Loy, and Sandra Skinner

Publication Support
Kevin Gregory

Journal of Huntington's Disease 11 (2022) S1–S46
DOI 10.3233/JHD229005
IOS Press

Abstracts

1

Real-World Treatment Patterns and Outcomes in Patients with Chorea Associated with Huntington's Disease Using Tetrabenazine or Deutetrabenazine in Combination with Antipsychotic Drugs

Daniel O. Claassen,[1] Hela Romdhani,[2] Rajeev Ayyagari,[2] Debbie Goldschmidt,[2] Sarah Zoye Moroz,[3] Adreanna B. Hernandez,[1] Nayla Chaijale,[4] Sam Leo[5]

[1]*Vanderbilt University Medical Center, Nashville, TN, USA*
[2]*Analysis Group, Inc., Boston, MA, USA*
[3]*East Tennessee State University, Johnson City, TN, USA*
[4]*Teva Branded Pharmaceutical Products R&D, Inc., Global Medical Affairs, West Chester, PA, USA*
[5]*Teva Branded Pharmaceutical Products R&D, Inc., Global Health Economics and Outcomes Research, Parsippany, NJ, USA*

Background: Real-world data on treatment patterns with vesicular monoamine transporter 2 inhibitors (VMAT2i; tetrabenazine [TBZ] or deutetrabenazine [DTBZ]) in combination with antipsychotic agents (APs) in patients with chorea in Huntington's disease (HD) are sparse, but could be informative for everyday practice.
Objective: To describe treatment patterns and outcomes with VMAT2i+AP in patients with chorea in HD in a real-world setting.
Methods: VMAT2i+AP treatment patterns, sequence, and outcomes were assessed retrospectively in adult patients with chorea in HD who received DTBZ or TBZ in combination with APs at Vanderbilt University Medical Center (2017–2021). Duration of combination treatment was assessed using Kaplan-Meier analysis. Effectiveness was assessed in patients with reported total maximal chorea (TMC) scores on a stable dose of DTBZ.
Results: Among patients using DTBZ+AP (n=57) or TBZ+AP (n=33), most common first treatments in treatment sequence were AP (37%), TBZ (27.4%), and DBTZ alone (17.8%); most common second treatments were DTBZ+AP (47.8%), TBZ+AP (18.8%), and DTBZ alone (18.8%). At 12 and 24 months, 71.9% and 50.9% of patients remained on DTBZ+AP combination treatment, and 66.7% and 27.3% remained on TBZ+AP combination treatment, respectively. Among patients with TMC efficacy data who added on DTBZ after an AP (n=13), 8 (61.5%) patients had improved TMC scores after reaching a stable DTBZ dose, 1 (7.7%) had no change, and 4 (30.8%) had worse scores.
Conclusions: Most patients using VMAT2i+AP continued on medication for at least 12 months, demonstrating real-world benefit. Prospective, controlled data on the role of VMAT2i+AP combination therapy are needed.

2

KINECT-HD: Results from a Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of Valbenazine for Chorea Associated with Huntington's Disease

Erin Furr Stimming,[1] Daniel O. Claassen,[2] Raja Mehanna,[3] Elise Kayson,[4] Jody Goldstein,[4] Hui Zhang,[5] Grace Liang,[5] Dietrich Haubenberger,[5] on behalf of the Huntington Study Group KINECT-HD Investigators and Coordinators

[1]*The University of Texas Health Science Center at Houston, McGovern Medical School, Houston, TX, USA*
[2]*Vanderbilt University Medical Center, Nashville, TN, USA*
[3]*UTHealth Houston, Houston, TX, USA*
[4]*Huntington Study Group, Rochester, NY, USA*
[5]*Neurocrine Biosciences, Inc., San Diego, CA, USA*

Background: Valbenazine, a potent and selective inhibitor of vesicular monoamine transporter 2, is currently approved for once-daily treatment of tardive dyskinesia.
Objective: This 12-week Phase 3 trial (KINECT-HD [NCT04102579]) was designed to evaluate the safety and efficacy of valbenazine in patients with Huntington's disease (HD)-related chorea.

Methods: Eligible adults were randomized 1:1 to double-blind treatment with placebo or valbenazine ≤80 mg, as tolerated. Primary endpoint was least-squares mean (LSM) change in the Unified Huntington's Disease Rating Scale (UHDRS) total maximal chorea (TMC) score from screening period-baseline (average of screening and baseline) to maintenance period (average of week 10 and week 12). Secondary endpoints included Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C) response (rating of "much improved" or better at week 12), and LSM change from baseline in NeuroQoL T-scores for lower extremity and upper extremity function. Safety assessments included treatment-emergent adverse events (TEAEs), vital signs, electrocardiogram, laboratory tests, and psychiatric assessments.
Results: Valbenazine treatment significantly reduced chorea severity, with a placebo-adjusted LSM TMC score reduction of 3.2 ($P<0.0001$). Clinician- and patient-rated global response rates were significantly higher for valbenazine vs. placebo: CGI-C (42.9% vs. 13.2%; $P<0.001$); PGI-C (52.7% vs. 26.4%; $P<0.01$). Neuro-QoL endpoints were not statistically significant. No clinically important changes in vital signs, electrocardiogram, or laboratory tests were found. No suicidal behavior or worsening of suicidal ideation was reported in valbenazine-treated participants.
Conclusions: In this Phase 3 trial, valbenazine was well-tolerated and associated with a robust and statistically significant improvement in chorea, along with substantial clinician- and patient-rated global improvement.

3

Motor Speech in Premanifest HD

Adam P. Vogel[1,2,3], Cheuk S. J. Chan[1], Geoffrey W. Stuart[3,4,5], Paul Maruff[6,7], Yenni Lie[8], Julie C. Stout[9,10]

[1]*Centre for Neuroscience of Speech, The University of Melbourne, Australia*
[2]*Division of Translational Genomics of Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tübingen, Germany & Center for Neurology, University Hospital Tübingen, Germany*
[3]*Redenlab, Inc., Melbourne, Australia*
[4]*Department of Cognitive Science, Macquarie University, Sydney, Australia*
[5]*School of Psychological Sciences, The University of Melbourne, Australia*
[6]*Cogstate, Inc., Melbourne, Australia*
[7]*Florey Institute of Neuroscience and Mental Health, Australia*
[8]*Statewide Progressive Neurological Disease Service, Calvary Health Care Bethlehem, Melbourne, Australia*
[9]*School of Psychological Sciences, Monash University, Melbourne, Australia*
[10]*Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University, Victoria, Australia*

Background: Clinical markers that show change in performance in people with Huntington's disease (HD) during the presymptomatic and prodromal stages remain a target of investigation in clinical medicine. Alongside genetic and neuroimaging initiatives, digital speech analytics has shown promise as a sensitive clinical marker of premanifest HD.
Objective: To investigate the sensitivity of digital speech measures for detecting subtle cognitive-linguistic and fine motor features in people carrying the expanded HD gene, with and without symptoms.
Methods: Speech data were acquired from 110 participants (55 people with the expanded HD gene, including 16 presymptomatic HD; 16 prodromal HD; 14 early-stage HD; 9 midstage HD; and 55 matched healthy controls). Objective digital speech measures were derived from speech tasks that fit along a continuum of motor and cognitive complexity. Acoustic features quantified speakers' articulatory agility, voice quality, and speech-timing. Subjects also completed the tests of cognition and upper limb motor function.
Results: Some presymptomatic HD (furthest from disease onset) participants differed from healthy controls on timing measures derived from the syllable repetition and monologue. Prodromal HD presented with reduced articulatory agility, reduced speech rate, and longer and variable pauses. Speech agility correlated with poorer performance on the upper limb motor test.
Conclusions: Tasks with a mix of cognitive and motor demands differentiated prodromal HD from their matched control groups. Motor speech tasks alone did not differentiate groups until participants were relatively closer to disease onset or symptomatic. Data demonstrated how ubiquitous behaviors like speech, when analyzed objectively, provide insight into disease-related change.

4

The Huntington's Disease-Health Index (HD-HI): A Novel, Clinically Relevant, Disease-Specific Patient-Reported Outcome Measure for HD

Anika Varma[1], Jamison Seabury[1], Spencer Rosero[1], Jennifer Weinstein[1], Olivia Brumfield[1], Christine Zizzi[1,2], Nuran Dilek[3], Danae Alexandrou[1], Alistair Glidden[1], Aaron Kaat[4], Michael McDermott[3,5], Ray Dorsey[1,3], Chad Heatwole[1,3]

[1]Center for Health + Technology, University of Rochester, Rochester, NY, USA
[2]Princeton University, Princeton, NJ, USA
[3]Department of Neurology, University of Rochester, Rochester, NY, USA
[4]Department of Medical Sciences, Northwestern University, Evanston, IL, USA
[5]Department of Biostatistics and Computational Biology, University of Rochester, Rochester, NY, USA

Background: The Huntington's Disease-Health Index (HD-HI) is a multifactorial, disease-specific patient-reported outcome measure designed to serially measure changes in disease burden during therapeutic trials, satisfy published U.S. Food and Drug Administration guidance, and facilitate drug-labeling applications.
Objective: To evaluate the internal consistency, known groups validity, and clinical sensitivity of the HD-HI.
Methods: We used Cronbach alpha scores to quantify the internal consistency of the HD-HI instrument and its subscales. We conducted known groups and area-under-the-curve (AUC) analyses using data from 201 individuals with HD to determine the ability of instrument total and subscale scores to differentiate between subgroups of patients with varying disease severity.
Results: The HD-HI consists of 13 subscales that measure patient perceptions of their emotional health, cognition, mobility and ambulation, activity participation, social performance, hand and arm function, fatigue, abnormal movements, social satisfaction, pain, daytime sleepiness, communication, and gastrointestinal health. The HD-HI has a high internal consistency with a Cronbach alpha of 0.99, and subscales have Cronbach alpha values that range from 0.78 to 0.97. The HD-HI total and subscale scores successfully differentiate between those with high vs. low total functional capacity (TFC), prodromal vs. manifest HD, employed vs. unemployed, and normal ambulation vs. mobility impairment. AUC analyses show that the HD-HI is capable of distinguishing between patients with high vs. low TFC (AUC=0.84) and prodromal vs. manifest HD (AUC=0.81).
Conclusions: The HD-HI is a highly sensitive, clinically relevant, and valid tool capable of measuring therapeutic gain during clinical trials with HD participants.

5

Potential for Combinatorial Therapeutic Approach Targeting BDNF and NMDA Receptors in the Treatment of Huntington's Disease

Mehul Mistry[1], Damini Patel[2], Aasmitha Chitturi[3], Pinkal Mistry[4], Danny Patel[5]

[1]California University of Science and Medicine, Colton, CA, USA
[2]Texas A&M University-College of Arts and Sciences, College Station, TX, USA
[3]University of Illinois-College of Pharmacy, Chicago, IL, USA, and Pomona Valley Medical Center, Pomona, CA, USA
[4]Bakersfield Heart Hospital, Bakersfield, CA, USA
[5]Encompass Health Care, USA

Background: Huntington's disease (HD) arises from the neurodegenerative effects of mutant HTT (mHTT), producing neurodegeneration via multiple mechanisms ultimately reducing neuron survival.
Objective: The aim of this study was to review the pathogenesis of HD and propose a combinatorial therapeutic approach targeting multiple factors contributing to HD progression.
Methods: Three searches were conducted to identify relevant literature focusing on therapeutic approaches to HD. The articles were screened by title and abstract, followed by a full-text review of selected articles.
Results: Eighteen articles were identified with focuses on therapeutics management using brain-derived neurotrophic factor (BDNF) agonism or N-methyl-D-aspartate receptor (NMDAR) antagonism. Molecular mechanisms were reviewed in each full-text article and used to propose a combinatorial therapeutic approach for treating HD using BDNF agonism and NMDAR antagonism.

Conclusions: Combinatorial therapies targeting BDNF, and extrasynaptic NMDAR may be effective in treatment of HD. BDNF agonism activates postsynaptic TrkB survival signaling pathways in coordination with memantine, an NMDAR antagonist. Memantine preferentially inhibits apoptotic signaling of extrasynaptic NMDAR while also maintaining the survival signaling of synaptic NMDAR. Coordinated therapy using a BDNF agonist and NMDA antagonist could improve single nucleotide polymorphism (SNP) survival and reduce excitotoxic apoptosis. HD is not defined by a single pathogenic process due to the diversely acting mutant protein. In animal models, 7,8-dihydroxyflavone (7,8-DHF) and memantine have shown to preserve neurological function by reducing striatum atrophy and improving neuronal survival. Continued research of effective therapeutic options targeting multiple unique mechanisms of HD should be conducted to determine whether combinatorial therapies have been overlooked in the treatment for HD.

6

Client Attitudes toward a Virtual Couples Retreat Post a Positive HD Gene Test Result

Bonnie L. Hennig-Trestman, Katherine Sherry, Debbi Fox-Davis

HD-Reach

Background: Only 5–20% of people at-risk for Huntington's disease (HD) pursue genetic testing. Psychological and social challenges are suggested factors that contribute to low testing utilization. There are limited resources offering follow-up guidance and support for people who have tested positive but are asymptomatic. Even fewer resources are available for significant others of people who test positive for the HD gene. This study sought to examine personal experiences of people who took part in a virtual retreat for couples after the person at-risk tested positive for the HD gene.
Methods: A free virtual two-hour "couples retreat" was offered to couples post-testing. The retreat was advertised via an HD advocacy organization using social media and marketing sent to U.S.-based HD testing centers and advocacy organizations. The retreat was created and facilitated by healthcare professionals who have expertise working with the HD community. Topics covered included sharing test results with others, planning for the future, and communication. Education, awareness, and support were offered. Participants had opportunities to interact and share experiences.
Results: A total of 14 people (seven couples) attended two separate retreats. Six clients provided feedback. All clients who completed the evaluation felt the retreat met their needs. Clients described the importance of validation of their feelings, feeling supported, and feeling that they were not alone.
Conclusions: Simple-to-replicate "couple-focused programs" offered to people who test positive for HD and their significant others is important post-testing for HD. Feedback received was overwhelmingly positive toward this type of program.

7

NT-0100D, a First-in-Class Peptide Nucleic Acid, Selectively Reduces Mutant Huntingtin in the Transgenic R6/2 Mouse Model

R.M. Friedlander[1], V. Di Caro[2], D.L. Carlisle[1], N.R. Monks[2], D.M. Stoltzfus[2], N.L. Bennet[2], Y. Suofu[1], J. Kim[1], F. Li[1], X. Wang[1], S.M. Yeh[1], O.V. Baranov[1], S.V. Baranov[1], B.A. Badeau[2], J.W. Gleaton[2], G.A. Cintrón-Rosado[2], R.R. Dyer[2], D.A. Stephan[2], W.R. Mann[2,] and S.E. Rojas-Caro[2]

[1]*Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, PA, USA*
[2]*NeuBase Therapeutics, Inc., Pittsburgh, PA, USA*

Background: Huntington's disease (HD) is a progressive autosomal dominant neurodegenerative disease caused by a CAG repeat expansion in the huntingtin (*HTT*) gene. NT-0100D, a PATrOL-enabled compound, crosses the blood-brain barrier (BBB) following subcutaneous delivery, invading the duplex genome, and directly engages the CAG expansion on the mutant huntingtin gene in a sequence-specific manner to inhibit transcription.
Objectives: Define allele-selectivity, dose-response, and cortico-striatal distribution of mutant huntingtin knock-down in the brains of R6/2 transgenic mice following subcutaneous delivery of NT-0100D.
Methods: Four-week-old female R6/2 and wild type B6-CBA mice were treated subcutaneously with NT-0100D b.i.w. x 8 weeks at 5, 10, and 21 mg/kg. The Rotarod test was performed weekly. At 12 weeks of

age, mutant and wild type brain *HTT* mRNA levels were determined by qRT-PCR. Brain HTT aggregates were quantified by immunohistochemistry (IHC) and western blotting. Neurofilament light chain (NfL) levels were measured in plasma.
Results: Subcutaneous delivery of NT-0100D inhibited transcription of *HTT* >75% across the brain in a dose-dependent manner ($p<0.001$). No change in wild type *HTT* was observed. Assessment of aggregates by IHC showed a dose-dependent decrease. Immunoblot analysis from brain showed a similar significant reduction. No reduction in wild type *HTT* was observed in livers of treated animals. NfL levels were unchanged with treatment. Dose-dependent trends in functional improvement were noted.
Conclusions: In a preclinical model, NT-0100D can be subcutaneously delivered, crosses the BBB, selectively reduces mutant huntingtin throughout the brain without inducing neurotoxicity, and has the potential to be a whole-body solution for patients with HD.

8

Improving the Communication Skills of Healthcare Professionals to Empower Families with Huntington's Disease

Filipa Júlio*[1,2] Astri Arnesen[1,3], Beatrice De Schepper[1,4], Dina De Sousa[1,5], Danuta Lis[1,6], Julia Oblitsova[1,7], Svein Olaf Olsen[1,3], Giorgos Papantoniou[1,8], Saija Ristolainen-Kotimäki[1,9], Marina Tretyakova[1,7], Zaynab Umakhanova[1,7]

[1]*European Huntington Association, Belgium*
[2]*Associação Portuguesa dos Doentes de Huntington, Portugal*
[3]*Landsforeningen for Huntingtons Sykdom, Norway*
[4]*Huntington Liga, Belgium*
[5]*Scottish Huntington's Association, UK*
[6]*Polskie Stowarzyszenie Choroby Huntingtona, Poland*
[7]*Orphan People, Russia*
[8]*Huntington's Disease Association of Cyprus, Cyprus*
[9]*Suomen Huntington Yhdistys RY, Finland*

Background: The relationship between families affected by Huntington's disease (HD) and healthcare professionals presents some challenges in Russia. Accordingly, the European Huntington Association (EHA) developed "Let Us Talk," a web-based course to train professionals on ways to effectively communicate and relate to HD families.
Objective: This work aimed to assess the impact of "Let Us Talk" on the communication skills of the course participants.
Methods: The online training was implemented over three Saturdays (12 hours total). Russian and non-Russian HD experts addressed topics such as verbal/nonverbal communication or HD-related communication changes. Original learning formats were used, like the screening of interviews with HD families. The EHA created a 20-item online questionnaire about communication skills in clinical settings, which was administered at the beginning of the training and one month later. The results of the two measurements were compared.
Results: One hundred eleven Russian healthcare professionals attended the course (79.2% neurologists). Fifty-nine answered the questionnaire at baseline and 30 answered it one month later. Significant differences were found in the behaviors adopted before and after the training. There was a decreased use of medical jargon and an increased recognition of the importance of giving patients time to express their questions and concerns.
Conclusions: "Let Us Talk" seems to have improved the communication skills of Russian healthcare professionals, who reported more appropriate behaviors toward HD families after the course. This training appears to be a good model for the EHA to replicate in other countries and enhance the doctor-HD patient relationship across Europe.

9

Assessing the Impact of a Communication Skills Training Experience on Healthcare Professionals Working with Huntington's Disease

Filipa Júlio*[1,2] Astri Arnesen[1,3], Beatrice De Schepper[1,4], Dina De Sousa[1,5], Danuta Lis[1,6], Julia Oblitsova[1,7], Svein Olaf Olsen[1,3], Giorgos Papantoniou[1,8], Saija Ristolainen-Kotimäki[1,9], Marina Tretyakova[1,7], Zaynab Umakhanova[1,7]

[1]*European Huntington Association, Belgium*
[2]*Associação Portuguesa dos Doentes de Huntington, Portugal*
[3]*Landsforeningen for Huntingtons Sykdom, Norway*
[4]*Huntington Liga, Belgium*
[5]*Scottish Huntington's Association, UK*
[6]*Polskie Stowarzyszenie Choroby Huntingtona, Poland*
[7]*Orphan People, Russia*
[8]*Huntington's Disease Association of Cyprus, Cyprus*
[9]*Suomen Huntington Yhdistys RY, Finland*

Background: Based on the communication challenges identified between families with Huntington's disease (HD) and healthcare professionals in

Russia, the European Huntington Association (EHA) developed "Let Us Talk," a web-based course to train professionals on ways to effectively interact with HD families. The online training was implemented over three Saturdays (12 hours total), involving Russian and non-Russian HD experts who addressed different HD-related communication topics.

Objective: This work aimed to assess the impact of "Let Us Talk" through the participants' feedback.

Methods: The EHA created an online survey to learn about the participants' appraisal of the course. The survey included open-ended and closed-ended questions, some requiring a rating from 1 (not interesting and not useful) to 4 (very interesting and very useful). Response rates and percentages were analyzed.

Results: There were 40 survey respondents. All reported their interest in attending future HD-related initiatives, and 70% indicated they would like a similar course format. The three highest rated presentations were from Russian professionals (weighted average ≥ 3.25). The videos with testimonies from HD families were the most appreciated content, together with the general debate about HD and communication in clinical settings (weighted averages = 3.30).

Conclusions: "Let Us Talk" has been well received by the Russian healthcare professionals, who seem keen to participate in future HD courses. Importantly, the course attendees favor presentations in their native language and value listening to HD families and other professionals. The feedback survey provides key information for the EHA to improve this training model and expand it to other countries.

10

Modelling Neurodegeneration Using a Human Isogenic System: A Next-Generation Approach to Study Huntington's Disease

Neil Matharoo, Tony Oosterveen, Oliver Dovey, Sejla Salic, Magdalena Gamperl, Tilmann Burckstummer, Anatoly Vasilyev, Karl Firth, Sarah Pokorny, Aris Siorentas, Arran Constantine, Marta Rucka, Tonya Frolov, Farah Patell-Socha, Thomas Moreau, Mark Kotter

bit.bio, Cambridge, UK

Background: Development of therapies to treat neuronal indications is hampered because less than 10% of findings derived from preclinical animal models can be translated to humans. Patient-derived induced pluripotent stem cells (iPSCs) enable generation of in vitro models that can recapitulate human disease phenotypes. However, conventional human iPSC (hiPSC) differentiation protocols are often lengthy, inconsistent, and difficult to scale. The lack of genetically matched controls for patient-derived models complicates the investigation of disease phenotypes. bit.bio has developed a robust iPSC reprogramming method (opti-ox) that overcomes these limitations and enables generation of mature cell types and isogenic disease models.

Objective: To generate a Huntington's disease (HD) model for use with isogenic, wild type ioGlutamatergic Neurons.

Method: We used CRISPR/Cas9-mediated genetic engineering to introduce a 50CAG expansion in the huntingtin *(HTT)* gene of our ioGlutamatergic Neurons. Mutant HTT proteins containing elongated polyglutamine stretches are aggregation-prone and have been reported to affect a range of neuronal subtypes, including cortical glutamatergic neurons.

Results: Characterization of the HD model showed that the expression profiles of HTT, and pan-neuronal and glutamatergic markers are highly similar to the ioGlutamatergic Neurons. In-depth phenotypic characterization of these cells is being performed to determine the differences in their transcriptome, neuronal activity, and mitochondrial functions.

Conclusions: Using opti-ox technology for the scalable and consistent production of hiPSC-derived isogenic disease models can advance the development of new therapeutics for Huntington's disease.

11

Key Results and Conclusions of the SIGNAL Phase 2 Study of Pepinemab as a Treatment for Early HD

Maurice Zauderer[1], Elizabeth Evans[1], Terry Fisher[1], Vikas Mishra[1], John Leonard[1], David Oakes[2], Kimberly Walters[3], Lisa Kowarski [3], Eric Siemers[4], Karl Kieburtz[2], Andrew Feigin[5]

[1] Vaccinex, Inc., Rochester, NY, USA
[2] University of Rochester, Rochester, NY, USA
[3] Statistics Collaborative, Washington, D.C., USA

[4] *Siemers Integration, LLC, Zionsville, IN, USA*
[5] *NYU Grossman School of Medicine, New York, NY, USA*

Background: The SEMA4D:plexin B1/B2 signaling pathway triggers reactive astrogliosis in the central nervous system. Stressed neurons upregulate SEMA4D and astrocytes intimately associated with neurons express both plexin B1 and B2 receptors. Binding of SEMA4D to those receptors results in astrocyte reactivity, including characteristic morphogenetic changes and downregulation of metabolic activity and recycling of neurotransmitters. Others have shown that the SEMA4D:plexin-B pathway is also involved in cross talk between astrocytes and microglia, hence SEMA4D plays a central role in overall glial reactivity.
Objective: We predicted that treatment with SEMA4D blocking antibody should prevent reactive transformation of astrocytes and reduce the associated changes, including decline in brain metabolic activity that is characteristic of HD progression. We investigated the impact of treatment on the course of motor and cognitive decline during clinical progression.
Methods: FDG-PET was employed in the SIGNAL study to detect changes in metabolic activity in brain of HD subjects. Motor activity was evaluated by UHDRS-TMS and Q-Motor assessments. A subset of two components of HD-CAB, OTS and PTAP, constituted a cognitive family, and the full HD-CAB was retained as an exploratory cognitive endpoint.
Results: Decline in glucose utilization observed in the placebo group was prevented and at least partially reversed by SEMA4D blockade with pepinemab. While the largest metabolic decline is observed in striatum in HD, a similar treatment effect was not observed for FDG-PET standardized uptake value ratio (SUVR) in caudate and putamen of either early manifest (EM) or late prodromal (LP) subjects. Since degeneration of medium spiny neurons in striatum is an early event in prodromal HD that continues following motor diagnosis, loss of such neurons could account for reduced glucose utilization that is not SEMA4D-dependent. Nevertheless, since caudate atrophy is significantly inhibited by pepinemab following 18 months of treatment, it appears that a SEMA4D-dependent mechanism becomes active also in striatum during continuing disease progression. In keeping with the absence of an early treatment effect on metabolic activity in striatum, we did not observe an effect on early motor dysfunction as detected by either UHDRS-TMS or Q-Motor assessments. Importantly, in parallel with metabolic effects in multiple cortical regions, several other endpoints indicated an impact of treatment on key cognitive domains, including learning during early manifest disease. The timing of SEMA4D-dependent cognitive and functional treatment outcomes is consistent with the complex kinetics of protective and pathogenic neuroinflammatory responses by glial cells.
Conclusions: In parallel with metabolic effects in multiple cortical regions, there appeared to be a clear effect of pepinemab treatment in early manifest disease on OTS (one sided p=0.028), a measure of executive function that is a key cognitive domain related to learning, as well as a direct effect on learning evident during sequential HD-CAB assessments. In contrast, we did not observe an effect on early motor dysfunction in either EM or LP populations as detected by either UHDRS-TMS or Q-Motor assessments. It is, however, possible that later stages of motor progression could be affected by treatment but are less prominent in the total functional capacity (TFC) ≥11 population enrolled in this study.

12

Neurobehavioral Symptoms of Huntington's Disease: The Impact of Personalized Psychopharmacology

Kasia Gustaw Rothenberg

Neurological Institute, Cleveland Clinic, Cleveland, OH

Background: Huntington's disease (HD) is a neurodegenerative disorder characterized by a triad of motor, cognitive, and psychiatric disturbances. Despite the known genetic link (symptomatic disease > 40 CAG repeats chromosome 4; *HTT* gene; autosomal dominant type of inheritance, "huntingtin" a product of the gene), no drugs currently exist to treat the underlying causes of this chronic, neurodegenerative condition. Chorea is a hallmark symptom of this disease, but behavioral and emotional dysregulation, as well as cognitive dysfunction, may precede motor symptoms. Changes in behavior and mental state often cause considerable distress and difficulty to patients and their caregivers. The neuropsychiatric and behavioral signs and symptoms of HD may present as a full spectrum of psychiatric illness, and most people with HD will experience multiple neuropsychiatric symptoms or disorders during the course of

their illness. These can be related to the underlying progressive neurodegeneration of the brain but can also be a psychological reaction to the knowledge of being a gene expansion carrier and the impairments of the disease. They may also arise as a side-effect of some HD medications. For example, some agents used to treat chorea may worsen apathy, depression, and other psychiatric symptoms. Although there is currently no cure for HD, it is a misconception that the neuropsychiatric symptoms of HD are untreatable. Treatments are available that can alleviate the neuropsychiatric symptoms of the disease.

Objective: Neurobehavioral symptoms in Huntington's disease occur early in the course of the disease and tend to be frequent, severe, and complex. The majority of patients require psychiatric assessment and psychopharmacological interventions. Most patients are in need of medication throughout their life span. Medication with mutually exclusive mechanisms of action is commonly used concomitantly. VMAT 2 inhibitors, which are used for the treatment of choreiform movements, may need to be administered in higher doses in CYP 450 2D6 fast metabolizers and may go into pharmacokinetic and pharmacodynamic interactions with antidepressants. For all the above reasons patients with Huntington's disease may benefit from guided psychopharmacology.

Methods: Demographics, genetic, and pharmacogenomic (GENOMIND; TEMPUS) information, as well as neurobehavioral parameters, were analyzed in 28 patients (10 M and 18 F, mean age 51, range 32–79, median 51) with symptomatic Huntington's disease (mean number of CAG repeats 44, range 38–62, median 43) diagnosed and treated in the Huntington's Disease Society of America (HDSA) Center of Excellence at The Cleveland Clinic (assessment between February 2019 and December 2021). Clinical questionnaires for psychiatric assessment of depression, suicidal ideation, anxiety, psychosis, compulsions, obsessions, irritability, and disruptive behavior, were completed, as was the Neuropsychiatric Inventory (NPI) for neurobehavioral assessment. Depression was quantitatively assessed by PHQ 9 (maximum score 27).

Results: Patients were evaluated twice at baseline and 6 weeks after medication changes guided by pharmacogenomic testing were implemented. Only 14% of patients didn't require changes in either their type or dose of medication. Change in medication was required in 19% of patients. Augmentation with medication was required in 27% of patients. A change in dose was required in 40% of patients. After implementing medication changes, 85% of patients reported improvement in symptom management. Only 2% of patients reported worsening in one or more symptoms. CYP2D6 variation determined VMAT2 dose for chorea management (higher target dose in ultra-rapid metabolizers). 85% of patients reported improvement in chorea symptoms. All examined patients but four (80%) reported a history of at least one episode of major depressive disorder. For all of them, we actively treated for depression (55% selective serotonin reuptake inhibitor (SSRI), 26% serotonin-norepinephrine reuptake inhibitor (SNRI), and 18% the other groups of antidepressants. 60% of patients were on two or more agents). After pharmacogenomics testing–driven changes, 88% of patients were in at least partial remission. According to the Patient Health Questionnaire (PHQ-9) (mean score 10.2, range 0–22, median 8), patients presented with only minimal (PHQ 1–4) or mild depression (PHQ 5–9) at the time of evaluation.

Conclusions: HD presents clinically with severe and complex neurobehavioral symptoms that frequently require pharmacological interventions. Pharmacogenomics testing may guide effective medication management in this group of patients.

13

Caregiver Burden: Evidence from the Huntington's Disease Burden of Illness (HDBOI) Study for Europe (EU-5) and US

Idaira Rodriguez-Santana[1], Rosa Willock[1], Samuel Frank[2], Barbara D'Alessio[3], Rebecca Fuller[4], Hayley Hubberstey[5], Cath Stanley[6], Elena Hernandez-Jimenez[1], Ricardo Dolmetsch[7], Sarah Ratsch[7], Talaha M. Ali[7]

[1]HCD Economics, Cheshire, UK
[2]Beth Israel Deaconess Medical Center, Boston, MA, USA
[3]LIRH Foundation, Rome, Italy
[4]CHDI Foundation, New York, NY, USA
[5]Huntington's Disease Youth Organization (HDYO), Kington, UK
[6]Huntington's Disease Association, Liverpool, UK
[7]uniQure Inc, Lexington, MA, USA

Background: Huntington's disease (HD) is a progressive neurodegenerative disorder that universally requires caregiver support over the patient's lifetime. Caregivers of people with Huntington's disease (PwHD) experience a large burden, which increases with disease progression.
Objective: This research provides a detailed profile of informal caregivers and explores the impact of HD on caregiver's health-related quality of life (HRQoL) using data from the Huntington's Disease Burden of Illness (HDBOI) study.
Methods: Demographic and HRQoL data on caregivers were extracted from the caregiver questionnaire of the HDBOI study. HRQoL was measured using EQ-5D-5L, and utility scores were computed using the UK value sets. Data were explored descriptively, and differences were assessed using ANOVA tests.
Results: The analytic sample had 471 informal caregivers (434 from Europe and 37 from US), with a mean age of 48.3 years. Most respondents reported to be the main caregiver (90.5%) of the PwHD and to live in the same household (85.4%). Most caregivers were a spouse/partner (50.8%), followed by a parent (20.6%) or a child (6.9%). A total of 24 (5.1%) caregivers were assisted by a contracted care professional. Caregivers who live in the same household with the PwHD reported worse HRQoL than those who do not, 0.87 vs. 0.91 [$p<0.05$]. Similarly, caregivers who received professional support reported better QoL scores than those who did not, 0.90 vs. 0.87 [$p>0.05$].
Conclusions: Our results offer a profile of caregivers of PwHD, quantify the humanistic burden associated with caregiving duties, and highlight that interventions aimed at supporting the needs of HD caregivers are required.

14

The Huntington's Disease Quality of Life Battery for Carers (HDQoL-Cs): Evidence from the Huntington's Disease Burden of Illness (HDBOI) Study for Europe (EU-5) and US

Idaira Rodriguez-Santana[1], Rosa Willock[1], Samuel Frank[2], Tiago Mestre[3], Jamie L. Hamilton[4], Cath Stanley[5], Louise Vetter[6], Elena Hernandez-Jimenez[1], Ricardo Dolmetsch[7], Sarah Ratsch[7], Talaha M. Ali[7]

[1]HCD Economics, Cheshire, UK
[2]Harvard Medical School/Beth Israel Deaconess Medical Center, Boston, MA, USA
[3]The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[4]CHDI Management/CHDI Foundation, New York, NY, USA
[5]Huntington's Disease Association, Kington UK
[6]Huntington's Disease Society of America, New York, NY, USA
[7]uniQure Inc, Lexington, MA, USA

Background: Huntington's disease (HD) progresses over time, impacting mental health, work productivity, and interpersonal relationships of the person with HD (PwHD) and their caregivers.
Objective: To explore the impact of HD on caregiver's quality of life (QoL) using the Huntington's Disease Quality of Life Battery for Carers (HDQoL-Cs) tool.
Methods: The short version of the HDQoL-Cs tool was part of the caregiver questionnaire of the HDBOI study. It has 23 items divided into two components: "satisfaction with life" and "feelings about living with HD." Each item ranges from 0 to 10 (higher scores reflecting better QoL), and component scores result from the mean score of corresponding items. Caregivers were categorized into groups according to the disease stage of the PwHD, based on the opinion of the treating physician. Differences in QoL were explored descriptively using analysis of variance (ANOVA) tests.
Results: The sample has 471 caregivers (434 European and 37 US), of which 36% were caregivers of early (ES), 35% of mid (MS), and 28% of advanced (AS) stage. Mean score of "*satisfaction with life"* decreased for more advanced stages: 5.95, 5.76, and 5.35 for ES, MS, and AS, respectively [$p<0.05$]. Satisfaction with treatment and social environment were the key items driving the satisfaction score. Regarding "*feelings about living with HD,"* the trend was similar: 5.87, 5.32, and 5.13 [$p<0.05$]. Stress and exhaustion were the most reported feelings experienced by caregivers.
Conclusions: Our results quantify the substantial humanistic burden associated with caregiving duties and highlight that the healthcare and psychosocial support needs of PwHD and their families remain largely unmet.

15

Suicidal Ideation and Sleep Disturbances by Disease Stage: Evidence from the Huntington's Disease Burden of Illness (HDBOI) Study for Europe (EU-5) and US

Idaira Rodriguez-Santana[1], Rosa Willock[1], Samuel Frank[2], Tiago Mestre[3], Astri Arnesen[4], Jamie L. Hamilton[5], Hayley Hubberstey[6], Michaela Winkelmann[7], Elena Hernandez-Jimenez[1], Ricardo Dolmetsch[8], Sarah Ratsch[8], Talaha M. Ali[8].

[1]HCD Economics, Cheshire, UK
[2]Harvard Medical School/Beth Israel Deaconess Medical Center, Boston, MA, USA
[3]The Ottawa Hospital Research Institute, Canada
[4]European Huntington Association, Norway
[5]CHDI Management/CHDI Foundation, New York, NY, USA
[6]Huntington's Disease Youth Organization HDYO, Kington, UK
[7]Deutsche Huntington-Hilfe e.V., Duisburg, Germany
[8]uniQure Inc, Lexington, MA, USA

Background: Sleep disturbances and increased suicide risk are common in people with Huntington's disease (PwHD), with rates significantly higher than those of the general population and other neurodegenerative diseases. However, the magnitude of these problems is still poorly understood.
Objective: To evaluate the presence of suicidal ideation and sleep disturbances for EU-5 and the US using data from the Huntington's Disease Burden of Illness (HDBOI) study.
Methods: The HDBOI is a retrospective, cross-sectional study in which physicians reported information on PwHD demographic and clinical characteristics, including suicidal ideation (at index date or previously). Moreover, PwHD completed the HDQLife Concern with Death and Dying tool and reported sleep disturbances through optional questionnaires. PwHD were classified as early (ES), mid (MS), or advanced stage (AS), according to the opinion of the treating physician.
Results: The sample had 2,094 PwHD (1,602 from Europe and 492 from US) of which were 40% ES, 33% MS, and 26% AS. Suicidal risk increased for more advanced stages: 11% of ES, 14% of MS, and 15% of AS were currently displaying suicidal ideation. HDQLife results (N=482) showed that 28% of PwHD felt anxiety about dying and 12% presented suicidal thoughts often or always. Over 47% of PwHD reported to have moderate or severe difficulty sleeping and the percentage increased to 68% for AS.
Conclusions: Sleep disturbances and suicidal ideation are elevated among PwHD and increase with disease progression. Interventions aimed at ensuring the provision of adequate mental health and suicide preventive services for PwHD are required to reduce the burden on PwHD.

16

HAP40 Is a Conserved Central Regulator of huntingtin and a Potential Modulator of Huntington's Disease Pathogenesis

Shiyu Xu[1], Gang Li[1], Xin Ye[1], Dongsheng Chen[1], Zhihua Chen[1], Zhen Xu[1], Moretti Daniele[4], Sara Tambone[4], Alessandra Ceccacci[4], Licia Tomei[4], Lili Ye[1], Yue Yu[1,6], Amanda Solbach[1,6], Stephen M. Farmer[1,7], Erin F. Stimming[2], George Mcallister[5], Deanna Marchionini[5], and Sheng Zhang[1,3,6 *]

[1]The Brown Foundation Institute of Molecular Medicine, McGovern Medical School at the University of Texas Health Science Center at Houston (UTHealth), Houston, Texas, USA
[2]Department of Neurology, HDSA Center of Excellence, McGovern Medical School at the University of Texas Health Science Center at Houston (UTHealth), Houston, Texas, USA
[3]Department of Neurobiology and Anatomy, McGovern Medical School at the University of Texas Health Science Center at Houston (UTHealth), Houston, Texas, USA
[4]Department of Translational and Discovery Research, IRBM SpA, Pomezia, Italy
[5]CHDI Management/CHDI Foundation, New York, NY
[6]Programs in Genetics and Epigenetics and Neuroscience, The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences, Houston, Texas, USA
[7]The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences, Houston, Texas, USA

Background: Perturbation of huntingtin (HTT)'s physiological function is one postulated pathogenic factor in Huntington's disease (HD). However, little is known about how HTT is regulated in vivo. In a proteomic study, we isolated a novel ~40kDa protein as a strong binding partner of *Drosophila* HTT and demonstrated it was the functional ortholog of HAP40, an HTT-associated protein shown recently

to modulate HTT's conformation but with unclear physiologic and pathologic roles. We showed that in both flies and human cells, HAP40 maintained conserved physical and functional interactions with HTT. Additionally, loss of HAP40 resulted in similar phenotypes as HTT knockout. More strikingly, HAP40 strongly affected HTT's stability, as depletion of HAP40 significantly reduced the levels of endogenous HTT protein while HAP40 overexpression markedly extended its half-life. Conversely, in the absence of HTT, the majority of HAP40 protein was degraded, likely through the proteasome. Further, the affinity between HTT and HAP40 was not significantly affected by polyglutamine expansion in HTT, and contrary to an early report, there were no abnormal accumulations of endogenous HAP40 protein in HD cells from mouse HD models or human patients. Lastly, when tested in *Drosophila* models of HD, HAP40 partially modulated the neurodegeneration induced by full-length mutant HTT while showing no apparent effect on the toxicity of mutant HTT exon 1 fragment. Together, our study uncovers a conserved mechanism governing the stability and in vivo functions of HTT and demonstrates that HAP40 is a central and positive regulator of endogenous HTT. Further, our results support that mutant HTT is toxic regardless of the presence of its partner HAP40, and implicate HAP40 as a potential modulator of HD pathogenesis through its multiplex effect on HTT's function, stability, and the potency of mutant HTT's toxicity.

17

Impact of Urban vs. Non-Urban Living on Quality of Life in Huntington's Disease

Abigail Ruffle[1], Bonnie Hennig-Trestman[1], Allison Tegge[2], Anita Kablinger[1], Robert Trestman[1]

[1] Virginia Tech Carilion School of Medicine, Roanoke, VA, USA
[2] Virginia Tech, Blacksburg, VA, USA

Background: Health-related quality of life (HRQoL) is a multidimensional tool commonly used to examine the impact of health status on quality of life in disorders such as Huntington's disease (HD). While many factors have been shown to impact HRQoL in HD, the impact of living in urban vs. non-urban settings is unknown.

Objective: The primary objective of this study is to examine whether living setting influences HRQoL in HD.
Methods: A retrospective cohort study was conducted using longitudinal data from the Enroll-HD trial. A hierarchical multiple linear regression was performed using quality of life as the dependent variable, residence (rural, village, town, city) and age as fixed independent variables, and participant as the random effect. The hypothesis tested was whether significant differences in HRQoL exist for people living in urban vs. non-urban settings.
Results: Data from North America (n=7,005) were analyzed. Significant interactions between age and both the physical and mental health components (PCS and MCS, respectively) of the 12-item Short Form Health Survey were identified. PCS declined with increasing age while MCS increased. There was no interaction between the PCS or MCS and residence type. Rural, village, and town residency types were combined. Physical health component scores declined faster in the group living in cities compared to those not living in cities. There was no difference in the rate of incline for MCS scores.
Conclusions: Age is an important demographic factor influencing HRQoL scores in HD. Other factors such as living setting may impact age-related changes in HRQoL.

18

The European Huntington's Disease Network (EHDN) Scientific Support

Christine Capper-Loup[1,2], Michael Orth[1,2,3], Anne Rosser[1,4], on behalf of EHDN Central Coordination

[1]European Huntington's Disease Network
[2]Neurozentrum Siloah, Switzerland
[3]University Hospital of Old Age Psychiatry and Psychotherapy, Bern University, Switzerland
[4]Cardiff University, Cardiff, UK

Background: The European Huntington's Disease Network (EHDN) is an independent nonprofit organization dedicated to advancing research, conducting clinical trials, and improving care for people affected by Huntington's disease (HD). To advance research, EHDN has developed a number of strategies.
(1) The **seed fund** scheme enables researchers to generate pilot data before applying for larger grants

from other organizations, or to conduct power calculations for clinical studies. There are two calls per year (March 1st and November 1st). The maximum sum available per project is EUR 50,000.
(2) The prospective, observational, longitudinal Registry study was conducted at 151 HD clinical sites across 17 European countries between 2004 and 2017. The data are available in the **Registry dataset (RDS)**. The format is similar to the Enroll-HD periodic dataset (PDS), using the same recoded IDs, if researchers want to analyze both data sets.
(3) The EHDN **Think Tank** complements and facilitates EHDN research initiatives such as working groups (WG) or task forces (TF). The think tank (a) interacts with WG and TF lead facilitators to help identify potential collaborators or funding opportunities for their research, or if they want to discuss scientific ideas, and (b) identifies key scientific questions in HD, some of which could be addressed scientifically by HD researchers through existing or new WGs/TFs.
(4) The EHDN **grant and collaborations manager** can support HD researchers in identifying potential funding opportunities and collaborations, including the fellowship program and HD educational webinars with the Movement Disorder Society.

19

Enroll-HD Platform Data Resources

Julia Keklak, Elena Ngangom, Christine Capper-Loup, on behalf of the Enroll-HD Platform Team

CHDI Foundation, Inc., New York, NY, USA

Background: Enroll-HD is a clinical research platform that includes at its core a global observational study of Huntington's disease (HD) families, followed annually. As of July 1, 2022, 27,899 participants have been recruited from 184 sites in 23 countries (Europe, North America, Latin America, Australasia). 21,044 of those participants are still current (i.e., no mortality/end form). Enroll-HD provides high quality coded clinical data and biosamples to qualified researchers in the HD research community via a straightforward request process (https://enroll-hd.org/for-researchers/). Every 1–2 years an easy-access Enroll-HD dataset (periodic dataset, PDS), including approximately 80% of the variables collected, is made available to qualified HD researchers. The next Enroll-HD PDS release is planned to be available in December 2022. The risk for participant identification from the PDS is low, but if researchers request non-PDS variables, the risk for participant identification may be increased. Therefore, a specified dataset request must be reviewed and approved by the Enroll-HD Scientific Review Committee. In addition to Enroll-HD, clinical data can be requested from the studies Registry, HDClarity, and TRACK-HD/ON. A large, easy-access Registry dataset (RDS) prepared in a format similar to the Enroll-HD PDS can augment the Enroll-HD PDS and thereby increase the total number of participants for modeling purposes. The RDS can be requested by contacting the EHDN Scientific and Bioethics Advisory Committee. Datasets are prepared free of charge. In addition to clinical data, the Enroll-HD platform distributes smaller imaging, brain morphometric/volumetric, genome-wide association study, RNAseq, MiSeq, methylation, and proteomics datasets collected across HD studies.

20

Enroll-HD Platform Biosample Resources

Julia Keklak, Elena Ngangom, Christine Capper-Loup, on behalf of the Enroll-HD Platform Team

CHDI Foundation, Inc., New York, New York, USA

Background: Enroll-HD is a clinical research platform that includes at its core a global observational study of Huntington's disease (HD) families who are followed annually. As of July 1, 2022, 27,899 participants have been recruited from 184 sites in 23 countries, in Europe, North America, Latin America, and Australasia. 21,044 of those participants are still current (i.e., no mortality/end form). In its capacity of clinical research platform, Enroll-HD provides high quality coded clinical data and biosamples to qualified researchers in the Huntington's disease research community via a straightforward request process (https://enroll-hd.org/for-researchers/). Due to its longitudinal nature, more than 70,000 blood kits have been collected in Enroll-HD to date. Currently, twelve different types of biosamples collected in three different studies (Enroll-HD, HDCSF/HD-Clarity, TRACK-HD/TRACK-ON) are available via the Enroll-HD platform, and additional biosample collections are in the planning stage. Non-renewable biosample resources require review and approval by

the Enroll-HD Scientific Review Committee (SRC) before release, whereas renewable resources can be released without SRC review. All biosample distributions come with a material, shipping and handling fee, and a biosamples use agreement must be signed before biosamples can be shipped. Currently available biosample resources include lymphoblastoid cell lines (LCLs), DNA from LCLs, DNA from whole blood, peripheral blood mononuclear cells (PBMCs), buffy coat, EDTA plasma, LiHep plasma, cerebrospinal fluid (CSF), cells from CSF, serum, PAXgene RNA, and buccal swabs.

21

The PERSPECTIVE Program: Evaluating the Effect of SAGE-718 on Cognitive Function in Patients with Huntington's Disease

Pranoti Pradhan[1], Julie Stout[2], Emily Lefler[1], Aaron Koenig[1], Jason Johannesen[1], Jennifer Petrillo[1], Sigui Li[1], Katrina Paumier[1], Jeffrey Wald[1], Mike Quirk[1], James Doherty[1]

[1]Sage Therapeutics, Inc., Cambridge, MA, USA
[2]School of Psychological Sciences and Turner Institute for Brain and Mental Health, Monash University, Melbourne, Australia

Background: SAGE-718 (NMDA-receptor positive allosteric modulator) is being investigated in patients with cognitive impairment due to Huntington's disease (HD).
Objective: The PERSPECTIVE Program is designed to evaluate SAGE-718's effect on cognitive performance/functioning in patients with HD. PERSPECTIVE comprises two double-blind, placebo-controlled Phase 2 studies (DIMENSION [NCT05107128; enrolling] and SURVEYOR [NCT05358821; enrolling]), and one Phase 3 open-label safety study (planned).
Methods: Patients with HD will be randomized 1:1 to receive daily oral SAGE-718 or placebo for 84 days (DIMENSION) or 28 days (SURVEYOR). DIMENSION's primary endpoint: Change from baseline (CFB) in HD Cognitive Assessment Battery (HD-CAB) composite score at day 84. Secondary endpoints: CFB in Unified HD Rating Scale (UHDRS) Independence Scale and UHDRS Total Motor Score, and safety/tolerability of SAGE-718. In SURVEYOR, a non-interventional cohort of matched healthy participants (HPs) will be assessed on performance scales for reference. Primary endpoint: Difference in baseline HD-CAB composite scores (HD vs. HPs). Secondary endpoints: Differences in baseline HD-CAB subset scores and other cognitive performance tests (HD vs. HPs); CFB in HD-CAB composite score and other cognitive performance tests at day 28 (patients with HD; SAGE-718 vs. placebo); and safety/tolerability of SAGE-718. Eligible patients completing DIMENSION or SURVEYOR, plus a de novo cohort of patients with HD (Total Functioning Capacity=13 and/or Montreal Cognitive Assessment score ≥26), may enroll in the open-label safety study.
Conclusions: PERSPECTIVE is designed to evaluate the efficacy and safety of SAGE-718 in patients with cognitive impairment associated with HD and provide an analysis of clinical meaningfulness of relevant cognitive endpoints.

22

Enroll-HD Platform Support for Industry and Academic Sponsors

Enroll-HD Platform Team, CHDI Foundation Inc., New York, New York, USA

Background: Enroll-HD is a global research platform with the infrastructure to support clinical trials and studies in Huntington's disease (HD). The prospective, observational, longitudinal Enroll-HD study at the core of the platform is active in 23 countries and has recruited 27,899 participants who have completed standardized clinical assessments and biosample collections at annual visits at 184 study sites (as of 1-Jul-22). This year marks the tenth anniversary since the first participant was enrolled.

The Enroll-HD platform makes resources available to the HD research community, including multiple clinical datasets and biosamples; advice on protocol design, including linking to the Enroll-HD study (nested study design); assistance with study feasibility, site identification and feasibility; participant recruitment; and site staff training and certification via the Enroll-HD clinical training portal.

Long-standing working relationships with the clinical sites have been built through the operational management and monitoring of Enroll-HD and platform studies, which enables well-informed site identification and feasibility assessment based on extensive knowledge of sites' capabilities, historic

performance, and information about access to potential participants. This site intelligence is supported by both the Enroll-HD HD Clinical Trial Site Certification scheme that assesses sites (within and outside Enroll-HD) against a set of standard minimum criteria for clinical trial participation, and the Enroll-HD study database that enables powerful in silico screening using study-specific inclusion and exclusion criteria to identify potentially eligible participants who can be considered for interventional trials.

23

The European Huntington's Disease Network (EHDN) (www.ehdn.org)

Jenny Townhill[1,2], Tim McLean[1], Jamie Levey[1,3], Anne Rosser[1,2], Patrick Weydt[1,4], Michael Orth[1,5,6], Christine Capper-Loup[1,5], on behalf of EHDN Central Coordination

[1]European Huntington's Disease Network
[2]Cardiff University, Cardiff, UK
[3]CHDI Foundation, New York, NY, USA
[4]University Hospital, Bonn, Germany
[5]Neurozentrum Siloah, Switzerland
[6]University Hospital of Old Age Psychiatry and Psychotherapy, Bern University, Switzerland

Background: The European Huntington's Disease Network (EHDN) is a nonprofit research network with the mission of advancing research, facilitating clinical trials, and improving clinical care in HD. EHDN creates a platform for clinicians, scientists, academics, patients, and family members to work together to achieve these goals. Membership in EHDN is open to those with an interest in and those who are directly affected by HD.

EHDN hosts a biannual meeting, one of the world's largest conferences dedicated to Huntington's disease.

EHDN working groups and task forces address key research topics, supported by the Think Tank experts with in-depth knowledge of HD and EHDN scientific activities. EHDN supports researchers by identifying funding opportunities and awarding seed funds. A fellowship exchange program facilitates training of young professionals from countries where HD care and facilities are developing.

EHDN offers review of clinical trial and study protocols, with endorsement given for protocols of high scientific and ethical quality. This endorsement is valued within the HD community as an independent expert opinion.

Clinical data and/or biosamples from the Registry study are available to researchers (see additional poster).

EHDN is governed by an executive committee overseeing activities and scientific strategy, and a Scientific and Bioethical Advisory Committee that advises on research proposals and clinical trial protocols.

EHDN Central Coordination manages operations, with regional staff (Lancos) linking the EHDN and clinical centers, liaising with the HD patient and research community, and monitoring Enroll-HD study and platform study data. EHDN is supported by the CHDI Foundation and collaborates closely with CHDI and the Enroll-HD platform.

24

JOIN-HD: The Juvenile Onset Initiative for Huntington's Disease

Jenna Heilman[1], Rebecca Mason[1], Marina Papoutsi[1,2], Beth Ann Griffin[1,3], Catherine Martin[1], Bonnie Hennig-Trestman[1,4], Oliver Quarrell[5], Lauren M. Byrne[1,6]

[1]Huntington's Disease Youth Organization, Kington, UK
[2]IXICO, London, UK
[3]RAND Corporation, Arlington, VA, USA
[4]Virginia Tech Carilion School of Medicine, Roanoke, VA, USA
[5]Sheffield Children's NHS Foundation Trust, Sheffield, UK
[6]University College London, London, UK

Background: Huntington's disease (HD) is a rare inherited neurodegenerative disorder with a typical onset between the ages of 30 and 50. Juvenile-onset Huntington's disease (JoHD), defined by the onset of symptoms before the age of 21, manifests differently from adult-onset HD. JoHD is thought to be present in approximately 5% of HD cases, although the exact prevalence is unknown. It has not been studied extensively.

JOIN-HD is a prospective, observational, multinational patient registry of individuals (both patients and caregivers) affected by JoHD. The primary objective of the registry is to identify individuals affected by JoHD and to map their locations globally. Secondary objectives include supporting focused research for this population and identifying the unmet needs of JoHD families to improve advocacy, care, and support. It is anticipated that JOIN-HD will serve as a tool to facilitate recruitment to future research and clinical trials through the identification of potentially eligible participants.

Pre-registration for JOIN-HD opened in Q1 2021, and Stage I is due to launch in Q4 2021. Participants will be invited to self-enroll and participate remotely via an electronic data capture portal. Stage I will capture participant demographics and information about the links participants have with the HD community. Two further stages of the registry are planned, with Stage II collecting data on medical history/experience of JoHD, and Stage III incorporating a clinician-led interview.

25

Stress, Loneliness, and Social Functioning in Adolescents and Young Adults At-Risk for Huntington's Disease

Abagail E. Ciriegio[1], Kelly H. Watson[1], Abigail L.B. Snow[2], Cara S. Guthrie[1], Marissa C. Roth[1], Abigail E. Pine[1], Anna C. Pflazer[2], Spencer Diel[2], Elizabeth Huitz[2], Lisa Hale[2], Daniel O. Claassen[2], and Bruce E. Compas[1]

[1] Vanderbilt University, Nashville, TN, USA
[2] Vanderbilt University Medical Center, Nashville, TN, USA

Background: Adolescents and young adults (AYA) at risk for Huntington's disease (HD) are exposed to substantial levels of stress, which can lead to increased psychiatric symptoms, loneliness, and decreased social connection due to feeling stigmatized.
Objective: This study sought to examine the associations among stress, loneliness, social functioning, and psychiatric symptoms in a sample of AYAs at risk for HD.
Methods: The sample included 38 AYAs ages 10–38 years (*M* age = 20.87). The Youth Self Report and Adult Self Report were used to assess psychiatric symptoms; the Responses to Stress Questionnaire was used to examine sources of HD-related stressors; loneliness was assessed using the UCLA Loneliness Scale; and social functioning was measured using the 36-Item Short Form Health Survey. Participant assent/consent was obtained in accordance with the institution's IRB.
Results: Nearly 40% of AYAs endorsed "Feeling isolated or different from peers" as a significant stressor in their lives. Further, those who endorsed social isolation as a stressor had significantly higher symptoms of anxiety and depression compared to those who did not (*t*=-2.35). Regression analyses revealed when the social isolation stressor was examined simultaneously with measures of loneliness and social functioning predicting psychiatric symptoms, the effect of social isolation stress was fully accounted for by loneliness (b=0.51) and social functioning (b=-0.32).
Conclusions: This study provides evidence that a significant portion of AYAs at risk for HD endorse feeling isolated and different from peers as a significant source of stress in their lives, which in turn takes a toll on their mental health through increased perceptions of loneliness and a decreased sense of social functioning. These findings point to important targets for intervention.

26

Huntington's Disease Presymptomatic Patients' Perception and Willingness to Participate in Clinical Trials

Seth Rotberg[1], B.J. Viau[1], Eric Miller[2], Deb Neville[2]

[1]Huntington's disease advocate
[2]Optio Biopharma Solutions

Background: A community survey was conducted in June 2022 to learn about the willingness of presymptomatic individuals to participate in clinical trials, along with the risks they'd be willing to take with hypothetical outcomes to halt disease progression.
Objective: Understand the benefits/risk desires of presymptomatic individuals along with understanding possible barriers for clinical trial recruitment of this demographic.
Methods: An online survey was distributed via social media for 1 month through personal pages and advocacy organizations. 164 U.S. participants who are either presymptomatic or at-risk explained their awareness of and willingness to participate in presymptomatic clinical trials as well as the levels of risk they would accept for effective medication.
Results: 73% of respondents visited a clinician less than once a year. 76% expressed a level of willingness to participate in presymptomatic clinical trials. Using a hypothetical thought experiment, individuals were willing to accept a mortality risk between 30% and 42% for a gene therapy that would slow symptoms by 90%.
Conclusions: Participants expressed a willingness to participate in clinical trials and accept a mortality risk for an effective treatment. Further studies should expand the sample size, increase questions about

risks/benefits of more potential treatments, and conduct in-depth interviews. While some trials have targeted participants earlier in disease onset, our research shows that presymptomatic and at-risk individuals demonstrate a desire to participate in clinical trials. HD stakeholders must learn more about this population and advocate for trials that include presymptomatic patients, effectively educate this population about opportunities, and begin recruitment and retention for trials.

27

Enroll-HD Study Status

Selene Capodarca, on behalf of the Enroll-HD Platform Team

Background: Enroll-HD is a clinical research platform that includes at its core an observational, prospective study of HD. Its objectives are: 1) expedite the conduct of clinical trials; 2) improve understanding of HD; and 3) foster good clinical care.

July 25, 2022, marks the 10-year anniversary since the first Enroll-HD participant. As of July 1, 2022, 27,899 participants have been recruited from 184 sites (155 are active) in 23 countries. 21,044 of those are still current (i.e., no mortality/end form), and 14,815 are active (i.e., have not missed two or more visits). Two sites have reached 1,000 participants enrolled.

Study data is monitored using a risk-based approach. Recoded data and biosamples are made available to researchers. The data and biosamples collected in Enroll-HD have led to significant scientific breakthroughs. There have been approximately 350 projects and 100 publications using Enroll-HD data and samples. The sixth periodic dataset will be released in December.

An increasing number of studies (platform studies, e.g., HDClarity) are using at least one area of Enroll-HD platform support, such as site feasibility, guidance on study design, potentially eligible participant listings, study setup support, and monitoring and data management.

The Enroll-HD Clinical Training Portal offers online training for the UHDRS Motor Certification, Good Clinical Practice (all users), and Enroll-HD Plasma Collection (Enroll-HD users). Training modules have recently expanded to support other studies hosted by the platform. The portal successfully enables faster, cost-effective start-up and standardization of training.

28

An Update on the PROOF-HD phase 3 trial: Pridopidine's Outcome on Function in Huntington's Disease

Ralf Reilmann[1], Andrew Feigin[2], Anne Rosser[3], Sandra Kostyk[4], Yael Cohen[5], Y Paul Goldberg[5], Michal Geva[5], Michael R Hayden[5,6], and the Huntington Study Group investigators and coordinators

[1] *George Huntington Institute, Muenster, Germany*
[2] *NYU Langone Health, New York, NY, USA*
[3] *University of Cardiff, Cardiff, Wales, UK*
[4] *Ohio State University College of Medicine, Columbus, OH, USA*
[5] *Prilenia Therapeutics*
[6] *CMMT, University of British Columbia, Vancouver, Canada*

Background: Pridopidine is a well-tolerated, oral Sigma-1 receptor (S1R) agonist. Human PET imaging shows pridopidine 45 mg BID, the dose evaluated in PROOF-HD, has selective and robust S1R occupancy. In preclinical models, S1R activation by pridopidine enhances multiple cellular processes impaired in HD, leading to neuroprotection.

In the exploratory PRIDE-HD Phase 2 trial, pridopidine 45 mg BID showed a beneficial effect vs. placebo (Δ0.87, p=0.0032) on total functional capacity (TFC) at week 52. TFC is a regulatory-accepted and validated scale for HD clinical progression. Post-hoc analysis shows this effect is driven by early HD patients (TFC 7–13, Δ1.16, p=0.0003). Responder analysis demonstrates that pridopidine reduced the probability of TFC worsening by 80% (p=0.002).

Objective: Evaluate the efficacy and safety of pridopidine 45 mg BID on TFC.

Methods: PROOF-HD is a 65-week, double-blind, placebo-controlled, Phase 3 trial assessing pridopidine 45 mg BID in early HD patients. Primary endpoint is change from baseline to week 65 in TFC. Secondary endpoints include proportion of patients with no TFC decline and changes to week 65 in Q-Motor, Total Motor Score (TMS), and the composite UHDRS. Plasma neurofilament levels are an exploratory endpoint.

PROOF-HD completed enrollment of 499 patients ahead of schedule in October 2021. As of July 27, 2022, low dropout (30/499, 6%) confirmed pridopidine's favorable tolerability and safety profile. On July 25, 2022, an independent safety monitoring committee (SMC) with accesses to all unblinded

data thoroughly reviewed the safety data and concluded that to date no safety signals of concern emerged. The SMC therefore recommends to continue the study without modification. Results are expected in early 2023.

29

A Concentration-QTc Analysis Shows Pridopidine Has a Concentration-Dependent Effect on QTc Interval, Which Is Not Clinically Relevant at the Therapeutic Dose of 45 mg BID

Michal Geva[1], Borje Darpo[2], Georg Ferber[3], Y Paul Goldberg[1], and Michael R Hayden[1,4]

[1]Prilenia Therapeutics
[2]Clario, Rochester, NY, USA
[3]Statistik Georg Ferber GmbH, Riehen, Switzerland
[4]CMMT, University of British Columbia, Vancouver, Canada

Background: Pridopidine is a highly selective Sigma-1 receptor (S1R) agonist currently being evaluated in the PROOF-HD Phase 3 trial.
Objective: To assess the effect of pridopidine on change from baseline in QTcF.
Methods: A concentration-QTc analysis (C-QTc) was performed using data from the exploratory PRIDE-HD Phase 2 trial in Huntington's disease (HD) patients. PRIDE-HD assessed four dosages of pridopidine (45, 67.5, 90, or 112.5 mg BID or placebo) for 52 weeks. Triplicate electrocardiograms with simultaneous plasma drug concentrations were determined pre- and post-dose in 402 HD patients. Cardiac-adverse events were analyzed from PRIDE-HD and from an integrated safety data set of three placebo-controlled trials in HD (HART, MermaiHD, and PRIDE-HD).
Results: Pridopidine shows a concentration-dependent effect on the QTcF interval (slope=0.012 ms/ng/mL; 90% confidence interval (CI): 0.0109–0.0127). The predicted QTc effect at 45 mg BID is 6.6 ms, with a two-sided 90% CI below 8 ms, which is of no regulatory concern (FDA considers QTc <10 ms low risk for Torsade de Pointes, TdP).

Across the integrated safety database, the rate of AEs for QT prolongation was higher in placebo vs. 45 mg BID (rate=0.013 vs. 0.005). No cases of TdP, and no increased risk for pro-arrhythmic events were reported at the clinical dose.
Conclusions: At the clinically relevant dose of 45 mg BID, pridopidine's effect on QT prolongation is not clinically relevant with no increased risk for pro-arrhythmic events.

30

Pridopidine Maintenance of Total Functional Capacity (TFC) Is Associated with Stabilization of Plasma Neurofilament Light (NfL) Levels

Michal Geva[1], Deniz Akinc Abdulhayoglu[2], Noga Gershoni-Emek[1], Y. Paul Goldberg[1], Bruno Boulanger[2] and Michael R. Hayden[1,3]

[1]Prilenia Therapeutics
[2]PharmaLex Belgium SA Mont-St-Guibert, Belgium
[3]CMMT, University of British Columbia, Canada

Background: Pridopidine is a Sigma-1 receptor (S1R) agonist in clinical development for Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS). S1R activation by pridopidine enhances neuroprotective pathways.

Increased levels of neurofilament light (NfL) protein indicate neuronal injury, serving as a biomarker that correlates with longitudinal disease progression. In other neurodegenerative diseases (e.g., multiple sclerosis), NfL reduction is associated with clinical efficacy. To date, no treatment has shown stabilization of NfL levels in HD.
Methods: PRIDE-HD (an exploratory Phase 2 study) assessed pridopidine for the treatment of HD for 1 year. Post-hoc analysis of early HD patients with available plasma samples (placebo, n=34; pridopidine 45 mg BID, n=31) at baseline and week 52 examined the effect of pridopidine on NfL levels (Simoa). The association between NfL and TFC (placebo n=41, pridopidine n=37) was modeled by a linear mixed model.
Results: There were similar demographics, CAG repeat length, and baseline TFC and NfL levels in placebo and pridopidine groups. Pridopidine shows TFC maintenance at 52 weeks ΔTFC +0.09 vs -1.0 in placebo (p=0.0006). Placebo shows the expected annual increase in NfL (ΔNfL+0.05 log2 pg/mL, similar to TRACK-HD (ΔNfL+0.037 log2 pg/mL). However, subjects on pridopidine show no annual increase in plasma NfL (ΔNfL -0.06 log2 pg/mL).

In the placebo group, increased NfL is associated with decreased TFC (p=0.008). In the pridopidine

group, NfL stabilization is associated with maintenance of TFC, significantly different from placebo (p=0.02). Significance is maintained after corrections for age (p=0.03), CAG length (p=0.02), BMI (p=0.03), and their combination (p=0.02).
Conclusions: Pridopidine 45 mg BID stabilizes plasma NfL levels in association with maintenance of TFC in early HD patients.

31

Analysis of Integrated Safety Data from Pridopidine Clinical Trials Demonstrates a Favorable Safety and Tolerability Profile at the Clinically Relevant Dose of 45 mg BID

Michal Geva[1], Y Paul Goldberg[1], Ralf Reilmann[2] and Michael R Hayden[1,3]

[1]Prilenia Therapeutics
[2]George Huntington Institute, Muenster, Germany
[3]CMMT, University of British Columbia, Vancouver, Canada

Background: Pridopidine is a highly selective and potent Sigma-1 receptor (S1R) agonist, being evaluated in the PROOF-HD, placebo-controlled, global Phase 3 trial. Primary endpoint is the effect of pridopidine 45 mg BID vs. placebo on change from baseline to week 65 in total functional capacity (TFC) in patients with early-stage HD.
Objective: To evaluate pridopidine's safety profile.
Methods: Pooled safety data from 22 trials assessing pridopidine at doses 10–112.5 mg BID were analyzed, encompassing safety data from 1,300 patients (~1,300 patient-years of exposure, including long-term data >5 years); 1,100/1,300 (85%) HD patients, and 981/1,300 (75%) treated with 45 mg BID, the dose assessed in PROOF-HD. Due to different placebo and pridopidine exposures, AE rate analyses, corrected for patient-years of exposure, were performed.
Results: The rate of common AEs was similar for placebo vs. 45 mg BID (rate respectively =2.35 vs. 1.82 events/patient years). Serious adverse events (SAEs) were reported in placebo and 45 mg BID groups (rate=0.07 and 0.18, respectively). Most SAEs were those commonly seen in HD.

As of July 27, 2022, PROOF-HD has a low dropout (30/499, 6%) rate, confirming favorable safety and tolerability profile. Blinded analysis of PROOF-HD revealed a total of 1,573 AEs reported. The majority (1520/1573, 97%) are determined to be mild-moderate. There are 46 SAEs, none of which are related to the study drug.
Conclusions: On July 25, 2022, an independent safety monitoring committee (SMC) with accesses to all unblinded data thoroughly reviewed the safety data and concluded that to date no safety signals of concern emerged. The SMC therefore recommends to continue the study without modification.

32

Development of Assessments for Later Stage Huntington's Disease: HD-Structures Interview of Function and HD Clinical Status Questionnaire

M.W. Roché[1], S. Capodarca[2], P. Winkowski[1], O.J. Handley[2], S. Frank[3], R.L.M. Fuller[1], M. Orth[4], J. Levey[1], E. Neacy[1], and C. Sampaio[1]

[1]CHDI Management/CHDI Foundation, Princeton, New Jersey, USA
[2]European Huntington's Disease Network
[3]Beth Israel Deaconess Medical Center, Boston, MA, USA
[4]Siloah AG, Bern, Switzerland

Background: There is a need for validated assessments for patients with later-stage HD.
Objective: This study aims to evaluate the clinimetric properties for two such measures: the HD Structured Interview of Function (HD-SIF) and HD Clinical Status Questionnaire (HDCSQ). Both assessments are administered to a companion either in-person or remotely (i.e., by phone contact with the companion), and the properties of these tests will be evaluated in a two-part study using the methods of Classical Test Theory (CTT) and Item Response Theory (IRT).
Methods: 170 dyads of people with Huntington's disease and their companion participants will be enrolled. The study includes two parts. In Part 1, we will use the methods of CTT to evaluate the HD-SIF, a structured interview designed to gather information for making ratings on the UHDRS '99 functional scales (total functional capacity (TFC), FAS and IS). In Part 2, we will use the methods of CTT and IRT to assess the clinimetric properties of the HDCSQ, a questionnaire designed specifically to capture information on disease milestones that occur during the later stages of HD, and the HD-SIF.

Status and Outlook: Four US sites, have recruited 15 dyads over a 5-month period. Preliminary results from Part 1 will be available by the end of 2022. Part 2 began in June 2022 with preliminary results expected by the end of 2023. Upon establishing the clinimetric properties of the scales, these assessments may be used for planning studies or incorporated into observational and interventional studies of HD.

33

Pridopidine Exerts Neuroprotective Effects Via Activation of the Sigma-1 Receptor

Michal Geva[1], Chiara Scaramuzzino[2], Sophie Lenoir[2], Romane A. Lahaye[2], Shao-Ming Wang[3], Hsiang-en Wu[3], Noga Gershoni-Emek[1], Frédéric Saudou[2], Tsung-Ping Su[3], and Michael R. Hayden[1,4]

[1]*Prilenia Therapeutics*
[2]*Grenoble Institut Neuroscience, Univ. Grenoble Alpes, Inserm, Grenoble, France*
[3]*Cellular Pathobiology Section, Integrative Neuroscience Research Branch, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, USA*
[4]*CMMT, University of British Columbia, Vancouver, Canada*

Background: Pridopidine is a selective Sigma-1 receptor (S1R) agonist in clinical development for Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS). The S1R modulates cellular processes commonly impaired in neurodegenerative disorders, including BDNF expression and autophagy.

Pridopidine demonstrates S1R-mediated neuroprotective effects. In HD neurons, pridopidine increases spine density, enhances mitochondrial function, and mitigates ER and oxidative stress. Pridopidine shows robust neuroprotection in human HD iPSCs and in mouse HD cortical neurons. Pridopidine's effects are exquisitely S1R-mediated, as its genetic deletion or pharmacological inhibition abolishes these effects.

Objective: To evaluate the effect of pridopidine on BDNF-TrkB signaling and autophagy.

Results: We used a microfluidic device that reconstitutes the corticostriatal network altered in HD. Primary neurons from *Hdh*$^{CAG140/+}$ HD mice provide a "disease-on-a-chip" platform ideal for investigating drug activity. Pridopidine rescued BDNF trafficking, resulting in an increased neurotrophin signaling at the synapse (~2-fold ($p<0.01$). This increased the capacity of HD neurons to release glutamate (~30%, $p<0.0001$), restore synapse homeostasis, and enhance p-ERK pro-survival signaling (~5-fold, $p<0.01$). Pridopidine's effect is abolished by the S1R antagonist NE-100.

In ALS, G_4C_2 repeats in the c9orf72 gene are the most common cause of familial ALS. The G_4C_2 expansion destabilizes the nucleopore complex inhibiting nucleocytoplasmic transport (NCT). NCT of the transcription factor EB (TFEB) is critical for the initiation of autophagy. Neuronal NSC34 cells overexpressing G_4C_2 repeats show impaired NCT of TFEB (~40%, $p<0.05$) leading to impaired autophagy (~30% reduction of LC3-II:LC3-I, $p<0.01$). Pridopidine rescues NCT of TFEB by ~90% ($p<0.01$) and enhances autophagy (50%, $p<0.05$), leading to neuroprotection (~12%, $p<0.001$).

Conclusions: Pridopidine enhances the availability of corticostriatal BDNF and upregulates autophagy via S1R activation, potentially leading to neuroprotection.

34

A Preliminary Huntington's Disease Registry at the University of South Florida

Rena Jiang[1], Stephen Aradi[1,2]

[1]*Morsani College of Medicine, University of South Florida, Tampa, FL, USA*
[2]*Department of Neurology, University of South Florida, Tampa, FL, USA*

Background: The University of South Florida Huntington's Disease Society of America Center of Excellence (USF HD CoE) sees HD patients across Florida. Disease registries support clinical care and research in specialty clinics.

Objective: To build a registry of patients in the USF HD CoE and provide preliminary descriptive analyses of the patient population.

Methods: Study data were collected and managed using REDCap electronic data capture tools hosted at USF. An EHR chart extraction was conducted using inclusion criteria of ICD-10 code G10 and HD CoE provider encounters between 1/1/2019 and 3/15/2022. R was used to generate figures and analyze data.

Results: 289 medical records were entered in the registry. 558 total motor score (TMS) and 150 total functional capacity (TFC) scores were recorded in 702 encounters. 74.7% of patients are white, 4.2% Hispanic, 2.1% black, 0.7% Asian, and the remaining are of unknown ethnicity. The median CAG length was 43, with a range of 36 to 67.

Between 3/2021 and 3/2022, the median TFC was 5 (range 0–13). TFC and TMS were negatively correlated (R^2 of 0.66).

Conclusions: This registry will allow the HD CoE to define our patient population along disease and demographic dimensions, to facilitate feasibility analyses for clinical research proposals and inquiries, and to support future patient-centered research substudies. Limitations of this registry include the selection bias associated with recruiting from a specialty clinic and the current restriction of current patient selection to retrospective encounters with existing ICD-10 diagnoses of HD. Future iterations will add encounters prospectively and include premanifest and at-risk patients.

35

Comparing Objective Performance with Self-report and Caregiver Ratings as a Measure of Anosognosia in HD

Shelby B. Hughes,[1,2] Emma Churchill[1,3], Anna Smirnova[1], Andrew Hall[1], Braden Culbert[1], Chase Snell[1], Zach Hutchings[1], Brenton Wright[1], Paul E. Gilbert[2,3], Jody Corey-Bloom[1,2]

[1]Department of Neurosciences, University of California San Diego, La Jolla, CA, USA
[2]San Diego State University/UC San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA
[3]Department of Psychology, San Diego State University, San Diego, CA, USA

Background: Individuals with Huntington's disease (HD) commonly experience anosognosia, a lack of awareness of deficits. Thus, it is important to examine the accuracy of self-report with caregiver report by comparing them with quantitative assessments.

Objective: To compare patient and caregiver report of cognitive and motoric symptoms versus objective performance measures.

Methods: The Anosognosia Scale (AS) was given to 33 manifest HD patients and their caregivers. The AS consists of eight items where individuals rate their global abilities relative to same-aged peers. Scores range from very impaired to excellent. Caregiver and patient scores were then correlated with objective measures.

Results: Caregivers' ratings of patients' cognitive and motoric abilities were more significantly correlated with objective measures compared to patients' ratings. Caregivers' AS item scores were highly correlated with objective measures of walking (Unified Huntington's Disease Rating Scale (UHDRS) tandem walking score [r=.57, p=.001] vs. patient [r=.39, p=.031]); dexterity (UHDRS pronation supination score [r=.55, p=.011] vs. patient [r=.18, p=.393]); speech (UHDRS dysarthria score [r=.55, p=.004] vs. patient [r=.03, p=.854]); memory (MoCA score [r=-.45, p=.048] vs. patient [r=-.11, p=.963]); attention (Trails Making Test A score [r=.58, p=.004] vs. patient [r=.08, p=.686]); and word retrieval (category fluency ([r=-.58, p=.004] vs. patient [r=-.02, p=1.00]). Additionally, the UHDRS total motor score (TMS) and the Mini Mental Status Exam (MMSE) were significant predictors of patient levels of anosognosia [TMS: F(1,29)=7.50, p=.010; MMSE: F(1,31)=5.40, p=.027].

Conclusions: Our findings indicate that caregivers may be better able to rate HD patients' cognitive and motor abilities than patients themselves. Cognitive and motor severity are also significant predictors of levels of anosognosia within HD.

36

Psychometric Properties of a Novel Brief Yet Comprehensive Behavioral Assessment in HD

Shelby B. Hughes,[1,2] Sameer Aboufadel[1], Anna Smirnova[1], Chase Snell[1], Emma Churchill[1,3], Andrew Hall[1], Vanessa Malcarne[2,3], Paul E. Gilbert[2,3], Jody Corey-Bloom[1,2]

[1]Department of Neurosciences, University of California San Diego, La Jolla, CA, USA
[2]San Diego State University/UC San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA
[3]Department of Psychology, San Diego State University, San Diego, CA, USA

Background: Individuals with Huntington's disease (HD) experience motoric, cognitive, and psychiatric dysfunction. These difficulties can cause maladaptive behaviors that can be distressing to family and

caregivers. Capturing these behaviors in clinical and research settings is crucial.
Objective: To develop and evaluate the psychometric properties of a new instrument, the Huntington's Disease-Behavioral Questionnaire (HD-BQ), which is brief yet comprehensive in assessing a broad range of behaviors in HD.
Method: Thirty items covering three domains of behavior (cognitive, psychiatric, functional) were generated. Items were scored on a 4-point Likert scale (completely disagree to completely agree) with higher scores indicating greater dysfunction. The self-report measure was piloted on a small sample of HD patients. Reliability (test-retest, internal consistency) and validity (convergent, discriminant, criterion) were evaluated.
Results: The HD-BQ demonstrated evidence for test-retest reliability (r=.81) and internal consistency (r=.96). Convergent validity was demonstrated by significant correlations with the Problem Behavior Assessment (PBA) (HD: r=.62; premanifest: r=.68) and the Hospital Anxiety and Depression Scale (HADS) (HD: r=.80; premanifest: r=.72). Evidence for divergent validity is seen through reduced correlations with dissimilar measures, including the MoCA (HD: r=-.16; premanifest: r=-.29) and the UHDRS Total Motor Score (HD: r=.12; premanifest r=.20). Criterion validity is shown with a receiver operator characteristic (ROC) curve indicating the HD-BQ outperformed the PBA and HADS in diagnostic capability of behaviors in HD.
Conclusions: Psychometric evidence supports that the HD-BQ, a brief, self-administered, paper and pencil 30-item test that requires minimal training to administer, is a valid and reliable instrument for the assessment of problem behaviors in HD.

37

Advancing Multidisciplinary Treatment and Care Coordination in Huntington's Disease

Karen Anderson[1], Martha Nance[2], Vicki L. Wheelock[3], Christine Goeschel[4], Melissa Eckroade[4], Lisa Hack[5], Cristen Querey[5], Donna Gabriel[5]

[1]Georgetown University School of Medicine, Washington, D.C., USA
[2]University of Minnesota, Minneapolis, MN, USA
[3]UC Davis Health, Sacramento, CA, USA
[4]MedStar Health Institute for Quality and Safety, Washington, D.C., USA
[5]Med-IQ

Background: MedStar Health Institute for Quality & Safety, in partnership with Med-IQ and faculty experts, developed a 12-month, multicomponent mentorship initiative in Huntington's disease (HD).
Objective: This educational initiative was designed to positively affect the future practice of multidisciplinary HD care teams across the United States and encourage nonspecialists to improve care for people with HD.
Methods: We conducted monthly group tele-mentoring sessions using the proven Project ECHO model as our primary educational framework. Project ECHO creates collaborative learning networks led by expert interprofessional teams who use a web-based videoconferencing platform to conduct virtual sessions with community-based providers. During each 1-hour session, faculty experts delivered a 10- to 15-minute didactic presentation, then used the remaining time to discuss challenging cases submitted by participants. The collaborators assessed changes in knowledge, competency, and performance pre- and post-initiative and gathered participant feedback using surveys and phone interviews.
Results: Clinicians from 19 sites participated. Sites included HD Centers of Excellence, community hospitals, and private practices. Learners included neurologists, nurses, social workers, physical/occupational therapists, genetic counselors, psychiatrists, and clinical researchers who collectively care for more than 200 patients with HD. Outcomes data and participant feedback revealed positive effects on learning and performance.
Conclusions: This initiative's high level of interactivity allowed for deep exploration of unique challenges that clinicians face in HD management, which is not easily achieved within more traditional educational frameworks. Clinicians who treat HD patients often feel professionally isolated, making ECHO an ideal framework for cultivating communities of practice and fostering continued engagement.

38

Trends in Chorea Severity Over Time by Huntington's Disease Stage

Erin Furr Stimming[1], Victor Sung[2], Shoshana Reshef[3], Rosa Willock[4], Rinat Ribalov[5], Sarah Brighton[4], Sam Leo[6]

[1]UTHealth, McGovern Medical School, Houston, TX, USA
[2]University of Alabama at Birmingham, Birmingham, AL, USA
[3]Teva Branded Pharmaceutical Products R&D, Inc., Epidemiology and Global Health Economics and Outcomes Research, Parsippany, NJ, USA
[4]HCD Economics Ltd., Cheshire, United Kingdom
[5]Teva Pharmaceutical Industries Ltd., Global Health Economics and Outcomes Research, Tel Aviv, Israel
[6]Teva Branded Pharmaceutical Products R&D, Inc., Epidemiology and Global Health Economics and Outcomes Research, Parsippany, NJ, USA

Background: Chorea, the most common motor symptom in adult-onset Huntington's disease (HD), negatively affects quality of life (QoL) and overall functional capacity in individuals with HD. Chorea has been reported to increase initially, plateau, then decrease over time; however, data assessing chorea severity by HD stage are limited.
Objective: To describe chorea severity over time in individuals with HD by HD stage.
Methods: Participants aged ≥18 years were identified from Enroll-HD, a global observational study for individuals with/at risk for HD (data cut 2013–31 October 2020). Participants in the manifest population were grouped by HD stage (Shoulson and Fahn staging) at baseline (total functional capacity [TFC] score 7–13/stage 1–2 [early], 3–6/stage 3 [middle], 0–2/stage 4–5 [late]). Chorea severity via total maximal chorea (TMC) score (0 [least severe]–28 [most severe]) was recorded at baseline and annual visits.
Results: Participants were grouped by HD stage (early, n=7,441; middle, n=2,330; late, n=1,120). At baseline, mean (standard deviation [SD]) TMC scores increased as HD stage progressed (early, 8.0 [4.7]; middle, 10.4 [5.8]; late, 10.6 [6.9]). Among participants with ≥4 years of follow-up (n=1,271), TMC score increased slightly over time for participants with early-stage HD, but plateaued at high levels in middle- and late-stage HD.
Conclusions: Chorea severity increased in early-stage HD and plateaued at a high level in middle- and late-stage HD, supporting the possibility of persistent chorea in late-stage HD. Future work is necessary to determine the impact of chorea on QoL and functional capacity in advanced HD.

39

Depression and Suicidality Throughout the Course of Huntington's Disease in the Enroll-HD Registry

Shoshana Reshef,[1] Erin Furr Stimming,[2] Victor Sung,[3] Rosa Willock,[4] Rinat Ribalov,[5] Sarah Brighton,[4] Sam Leo[6]

[1]Teva Branded Pharmaceutical Products R&D, Inc., Epidemiology and Global Health Economics and Outcomes Research, Parsippany, NJ, USA
[2]UTHealth, McGovern Medical School, Houston, TX, USA
[3]University of Alabama at Birmingham, Birmingham, AL, USA
[4]HCD Economics Ltd, Cheshire, United Kingdom
[5]Teva Pharmaceutical Industries Ltd., Global Health Economics and Outcomes Research, Tel Aviv, Israel
[6]Teva Branded Pharmaceutical Products R&D, Inc., Global Health Economics and Outcomes Research, Parsippany, NJ, USA

Background: High rates of depression have been reported in Huntington's disease (HD); however, real-world data on their course are lacking.
Objective: To describe the baseline frequency of depression and suicidality among patients with HD, stratified by HD stage and chorea severity.
Methods: Enroll-HD is a global observational registry for participants with/at risk for HD. Data were collected (data cut 2013–31 October 2020) using the Hospital Anxiety and Depression scale (HADS), Problem Behavioral Assessment ([PBA] binary scale, and Columbia-Suicide Severity Rating Scale (CSSRS). Participants were grouped by HD status (manifest, pre-manifest, non-HD) and stage via total functional capacity score and Shoulson and Fahn staging [1]: 7–13/stage 1–2 (early), 3–6/stage 3 (middle), 0–2/stage 4–5 (late), and by chorea severity (total maximal chorea [TMC] score).
Results: Depression was more severe in the manifest group (n=10,917; mean [standard deviation, SD] HADS: 6.1 [4.2]) vs. non-HD (n=4,996; 3.4 [3.3]) and pre-manifest (n=5,173; 3.6 [3.5]) groups, with an increasing trend toward later HD stages (early [n=7,441], 5.7 [4.0]; middle [n=2,330], 7.3 [4.4]; late [n=1,120], 8.4 [4.9]). Depression severity was

high in all TMC strata, with no clear trend (TMC=0–7 [n=5,055], 6.2 [4.2]; TMC=8–14 [n=4,374], 6.0 [4.2]; TMC=15–21, [n=1,310], 6.4 [4.1]; TMC=22–28 [n=164], 7.6 [4.1]). PBA and CSSRS scores exhibited similar trends.
Conclusions: Depression and suicidality were notably higher in the manifest vs. non-HD and pre-manifest groups, regardless of disease stage. Depression and suicidality were common in participants with chorea and did not correlate with chorea severity.

40

Baseline Characteristics and Treatment Patterns of a Global Huntington's Disease Population Stratified by Chorea Severity

Victor Sung,[1] Erin Furr Stimming,[2] Shoshana Reshef,[3] Rosa Willock,[4] Rinat Ribalov,[5] Sarah Brighton,[4] Sam Leo[6]

[1]University of Alabama at Birmingham, Birmingham, AL, USA
[2]UTHealth, McGovern Medical School, Houston, TX, USA
[3]Teva Branded Pharmaceutical Products R&D, Inc., Epidemiology and Global Health Economics and Outcomes Research, Parsippany, NJ, USA
[4]HCD Economics Ltd, Cheshire, United Kingdom
[5]Teva Pharmaceutical Industries Ltd., Global Health Economics and Outcomes Research, Tel Aviv, Israel
[6]Teva Branded Pharmaceutical Products R&D, Inc., Global Health Economics and Outcomes Research, Parsippany, NJ, USA

Background: Though multiple treatment options exist for Huntington's disease (HD)-associated chorea, there are little real-world data on treatment patterns, especially across disease trajectory and variation by chorea severity.
Objective: To describe baseline characteristics and treatment patterns in individuals with HD-associated chorea by chorea severity.
Methods: Participants were adults from Enroll-HD, a global observational registry for patients with HD and their families (data cut 2013–31 October 2020). Data on age, sex, total maximal chorea (TMC) score, treatment for chorea (specifically vesicular monoamine transporter 2 [VMAT2] inhibitors and antipsychotic agents [APs]) were collected at baseline. Participants were grouped by chorea severity, determined by baseline TMC score (0 [least severe]–28 [most severe]).
Results: Of 10,903 participants (TMC 0–7, n=5,055; 8–14, n=4,374; 15–21, n=1,310; 22–28, n=164), 51% were female and mean age at baseline was 53.0 years. VMAT2 inhibitor use at baseline was 14.9% of all patients, AP use at baseline was 34.5% overall, and 5.8% of all patients had combined use of VMAT2 inhibitors with APs. Use of VMAT2 inhibitors and APs (alone or together) increased with chorea severity.
Conclusions: Use of VMAT2 inhibitors and APs was low for all chorea categories, but increased incrementally with severity. Use of VMAT2 inhibitor/AP combinations at baseline was less common but increased as chorea severity increased. These data suggest that HD-associated chorea may be undertreated. More data are needed to understand the utility of VMAT2 inhibitors and APs, alone and in combination, for alleviating HD-associated chorea and psychiatric comorbidities.

41

Huntingtin Secretion in a Free Form and in Extracellular Vesicles Modulates Neuronal Activity and Is a Potential Biomarker for Huntington's Disease

Inês Caldeira Brás[1,2], Yuanyun Xie[1], Tiago Fleming Outeiro[2], Amber Lee Southwell[1]

[1]Burnett School of Biomedical Sciences, University of Central Florida, Orlando, Florida, USA
[2]Department of Experimental Neurodegeneration, Center for Biostructural Imaging of Neurodegeneration, University Medical Center Göttingen, 37073 Göttingen, Germany

Background: Identification of mutant huntingtin (HTT) in the cerebrospinal fluid (CSF) of Huntington's disease patients and its correlation with motor and cognitive symptoms demonstrates the importance of measuring extracellular HTT in clinical trials. Several mechanisms have been proposed for HTT release from cells, as in a free form but also enclosed in extracellular vesicles (EVs). However, their relative contribution to HTT levels in the extracellular space and in CSF, and overall effect on neuronal function, is still unclear.
Objective: Investigate HTT levels in EV subtypes, as ectosomes and exosomes, and their potential role as disease biomarkers.
Methods: Measurement of HTT levels in the extracellular space and in the CSF. Isolation of EV

subtypes combined with comprehensive proteomic analysis and imaging of EV internalization. Assessment of EV extracellular effects using multichannel electrophysiological recordings.
Results: Nondegenerating neurons secrete both wild-type and mutant HTT (mHTT), which contributes to deposition of mHTT in CSF. This process occurs in the absence of neurodegeneration, and HTT can enter the CSF by both passive release and active secretion. Furthermore, HTT is secreted in a free form but also in ectosomes and exosomes. Using multielectrode array recordings, we show that neurons treated with mutant HTT display greater impairment in the coordinated network activity correlated with the toxic effects of polyglutamine expansion.
Conclusions: HTT release is a normal process occurring in the absence of pathogenesis, though modulated by disease. Importantly, we demonstrate the unexplored potential toxic effect of extracellular mHTT because it modulates neuronal function. Understanding the mechanisms involved in HTT secretion and its potential function in the extracellular space will be important for the development of improved therapeutic strategies.

42

A Comparison of Self-Report and Informant-Report Irritability Scale in Huntington's Disease Patients with Evidence of Irritability or Aggression

Joyce En-Hua Wang[1], Neal Simon[2], Mike Brownstein[2], Hilda Maibach[2], Karen Anderson[3]

[1]Georgetown University School of Medicine, Washington, D.C., USA
[2]Azevan Pharmaceuticals, Inc., Bethlehem, PA, USA
[3]Department of Neurology & Department of Psychiatry, Georgetown University, Washington, D.C., USA

Background: Irritability is a prevalent neuropsychiatric symptom in Huntington's disease (HD), but there is no gold standard for its measurement. The Irritability Scale (IS), developed specifically for HD, has patient and informant versions. Previous studies reported variable interrater agreement, making the impact of irritability on functioning unclear. Further validation is needed to use IS as a trial endpoint for behavioral symptoms.
Objective: This study evaluated the agreement between IS reported by patients and informants and explored IS as a correlate of functional capacity.
Methods: Baseline irritability was characterized with IS in patients with confirmed irritability in the STAIR (Safety, Tolerability, and Activity of SRX246 in Irritable Subjects with Huntington's Disease) trial. The interrater agreement on IS was determined with Pearson's correlation. Univariate linear regression was performed for the Unified Huntington's Disease Rating Scale (UHDRS) total functional capacity (TFC) score.
Results: The interrater agreement on IS was significant although modest ($r = 0.32$) and varied by item ($r = 0.07–0.51$). A subscale was derived from four items with the highest interrater agreement – "Do you yell a lot?", "Do you insist on having your own way?", "Do you pout if things don't go your way?", and "Do you consider yourself to be irritable?" Greater functional decline on TFC correlated with more severe irritability reported by informants on the four-item IS subscale but not with informant report or patient self-report on the IS.
Conclusions: Substantial variability in item performance suggests that future research may be better served through development of an abridged IS.

43

A Phase 2 Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenous ANX005 in Patients with, or at Risk of, Manifest Huntington's Disease (HD)

Rajeev Kumar[1], Daniel O. Claassen[2], Ann Mongan[3], Benjamin Hoehn[3], Ping Lin[3], Ellen Cahir-Mcfarland[3], Lori Taylor[3], Priya Chandra[3], Ted Yednock[3], Henk-Andre Kroon[3]

[1]Rocky Mountain Movement Disorders Center, Englewood, CO, USA
[2]Vanderbilt University Medical Center, Nashville, TN, USA
[3]Annexon Biosciences, South San Francisco, CA, USA

Background: ANX005 is a humanized monoclonal antibody designed to inhibit C1q.
Objective: Report final results of ANX005-HD-01, a phase 2 study of patients with or at risk of manifest HD.

Methods: Eligible patients (CAP>400) received intravenous ANX005 every 2 weeks through week 22 (NCT04514367). Endpoints were assessed on-treatment through week 24, with off-treatment follow-up through week 36. Primary objectives included safety/tolerability, pharmacokinetics (PK), and C1q, C4a, and NfL levels (CSF and plasma). Exploratory objectives of clinical efficacy included cUHDRS and total functional capacity (TFC).
Results: All safety population (n=28) patients experienced transient infusion-related reactions during the first dose, mainly transient maculopapular rash. Two serious adverse events occurred, lupus-like presentation and idiopathic pneumonitis, which reversed or improved upon treatment discontinuation. Steady-state PK were achieved by week 6 in the blood and CSF. ANX005 demonstrated complete and durable C1q inhibition in CSF and serum, consistent with drug levels. Mean plasma and CSF NfL levels for 24-week completers (n=23) tracked with NfL natural history. Clinical disease progression was stable in the overall patient population throughout the entire 9-month study as measured by mean change in cUHDRS and TFC relative to baseline. Subgroup analysis indicated that patients with high baseline C4a/C4 (n=12) exhibited clinical improvement in cUHDRS at all timepoints, with a significant difference from patients with low baseline C4a/C4 (n=11) at week 24 (p=0.037). Consistent separation in TFC between the two subgroups was observed throughout the study.
Conclusions: ANX005 was generally well-tolerated, maintained full target engagement, and showed clinical improvement in a subgroup of HD patients.

44

Challenges and Advances in Cerebrospinal Fluid HTT Detection: In Support of Relative Quantification

Rachel J. Harding[1], Yuanyun Xie[2], Nalini Potluri[2], Cheryl H. Arrowsmith[1], Blair R. Leavitt[3], Douglas Langbehn[4], Amber L. Southwell[2]

[1]Structural Genomics Consortium, University of Toronto, Toronto, Canada
[2]Burnett School of Biomedical Sciences, University of Central Florida, Orlando, FL, USA
[3]Centre for Molecular Medicine and Therapeutics, University of British Columbia, Vancouver, BC, Canada
[4]Department of Psychiatry, University of Iowa, Iowa City, IA, USA

Background: With continuing development of huntingtin (HTT)-lowering therapies, advances in huntingtin detection for assessment of target engagement are required. In current clinical trials, cerebrospinal fluid (CSF) mutant HTT (mHTT) concentration is quantified absolutely using a single monomeric protein standard.
Objective: To better understand what treatment-induced changes in CSF mHTT mean about the brain.
Methods: We are using immunoprecipitation and flow cytometry (IP-FCM) in combination with multiple model systems to investigate the origins of HTT protein in the CSF, as well as its mechanisms of entry, and a series of recombinant HTT proteins to investigate factors that modulate assay signal.
Results: We have found that HTT is secreted by neurons in both health and disease and that both wild-type and mHTT are present in CSF. Additionally, we have found that there is a bias toward striatal contribution to CSF mHTT with disease progression, likely resulting from a combination of the early neurodegeneration and polyglutamine tract expansion observed in the striatum. This suggests that this measure can act as a pharmacodynamic biomarker of striatal HTT lowering despite the relatively small proportion of striatal neural tissue. However, we have found that HTT concentration, conformation, fragmentation, protein interaction, and polyglutamine tract length affect ultrasensitive assay signal intensity, indicating that absolute HTT quantitation in heterogeneous biological samples is not possible with current technologies using a single standard protein.
Conclusions: Based on these observations, we recommend that only relative mHTT quantitation using normalized arbitrary units of assay signal intensity be used for the assessment of central nervous system HTT lowering in ongoing clinical and preclinical studies.

45

Audio Analysis of Acoustic and Linguistic Features in Huntington's Disease (Audio-HD)

L.A. Sierra[1], C. Ullman[1], K. Hildebrand[1], J. Dierker[1], M. Mwangi[1], H. O'Connell[2], S. Frank[1], S. Laganiere[1]

[1]Beth Israel Deaconess Medical Center, Boston, MA, USA
[2]Canary Speech, Provo, UT, USA

Background: The diagnosis of Huntington's disease (HD) is based primarily on the motor exam component of the Unified Huntington's Disease Rating Scale (UHDRS). The UHDRS has a single item to grade dysarthria from 0 to 4 (normal to anarthria); however, automated speech feature detection could be a more sensitive biomarker of disease onset or progression.
Objectives: Using a data-driven exploratory approach, we sought to identify the features of speech that differentiated HD from controls using software developed by Canary Speech.
Methods: HD participants (n=26) and healthy controls (HC, n=21) were matched for sex, age, and education. Participants completed an 8-minute tablet-based protocol (Audio-HD) that included open-ended questions, passage reading, narrative prompt, picture description, and audio recording of the Stroop Color and Word Test (SCWT).
Results: The HD cohort's average UHDRS total motor score was 13.5 (SD=13.14) and expanded CAG repeat length 43.2 (SD=3.34). Welch's t-test (95% confidence interval) identified >1,000 features of speech that differentiated HD from controls. Features acquired during SCWT and passage reading prompts identified the highest number of significant differences between cohorts. Among many others, speech dynamics ($P = 0.033$), duration per word ($P < 0.001$), words per second ($P < 0.001$), bandwidth ($P = 0.005$), and contrast ($P < 0.001$) were significant.
Conclusions: The Audio-HD protocol using Canary Speech is a sensitive assessment for detecting speech changes in HD. Identified features will be integrated into learning models to generate speech biomarkers with the highest sensitivity for early changes in HD.

46

Cognitive Function, Stress Reactivity, and Psychiatric Symptoms in Adolescents at Risk for Huntington's Disease

Kelly H. Watson[1], Abagail E. Ciriegio[1], Abigail Snow[2], Anna Pfalzer[2], Cara Guthrie[1], Marissa Roth[1], Abigail Pine[1], Daniel O. Claassen[2], and Bruce E. Compas[1]

[1] Vanderbilt University, Nashville, TN, USA
[2] Vanderbilt University Medical Center, Nashville, TN, USA

Background: Children of parents with Huntington's disease (HD) are faced with significant stress, placing them at increased risk for emotional and behavioral problems. Research has shown that reactivity to stress (e.g., emotional and physiological arousal) and psychiatric symptoms (e.g., depression, anxiety) experienced in response to stress can interfere with cognitive functioning. These processes have particular relevance for adolescents in families affected by HD, as adolescence is a period of significant change and challenge.
Objective: To examine associations of stress reactivity and depression and anxiety symptoms with cognitive functioning in adolescents at risk for HD.
Methods: Twenty-five adolescents ages 8–17 years old ($M = 13.44$; 52% female) at risk for HD were administered the fluid cognition subtests from the National Institutes of Health Toolbox to obtain a Fluid Cognition Composite (FCC) Age-Corrected score. Parents reported on adolescents' stress reactivity using the Responses to Stress Questionnaire and symptoms using the Child Behavior Checklist. Parental consent and adolescent assent were obtained in accordance with the informed consent regulations at the institution.
Results: In bivariate correlation analyses, lower scores for adolescents on the FCC were associated with higher levels of stress reactivity ($r = -.50$, $p < .01$) and higher symptoms of depression ($r = -.44$, $p < .05$) and anxiety ($r = -.47$, $p < .05$). Adolescents' age was unrelated to cognitive functioning, stress reactivity, or psychiatric symptoms.
Conclusions: Findings suggest that greater stress reactivity and psychiatric symptoms are associated with lower cognitive functioning. These findings extend research by examining factors that may exacerbate risk for cognitive impairment in adolescents at risk for HD. These findings also highlight possible avenues for behavioral intervention to indirectly improve cognition. Future research should examine these processes in a longitudinal design.

47

Digital Monitoring of Motor Symptoms in Huntington's Disease: Evaluation of Digital Biomarkers in Large-Scale Longitudinal Data Collection

Cedric Simillion[1], Louis-Solal Giboin[1], Johannes Rennig[1], Fiona C. Kinsella[2], Rosanna Tortelli[2], Florian Lipsmeier[1], Edward J Wild[2], Peter McColgan[3], Michael Lindemann[1], Jonas Dorn[1]

[1]Roche Pharmaceutical Research and Early Development, pRED Informatics, F. Hoffmann-La Roche, Basel, Switzerland
[2]Huntington's Disease Centre, UCL Queen Square Institute of Neurology, University College London, London, UK
[3]Roche Products Ltd., Welwyn Garden City, UK

Background: The Roche Huntington's disease (HD) digital monitoring platform (dMP), consisting of smartphone-based active tests and smartphone- and smartwatch-based passive monitoring, has previously shown good test-retest reliability and cross-sectional validity. Since then, longitudinal data have become available to further evaluate the dMP.
Objective: Identify optimal features per active test using longitudinal digital biomarker data from the Roche HD dMP collected across the tominersen program (HD Open-Label Extension [OLE] [NCT03342053], HD Natural History Study [NHS] [NCT03664804]), including GENERATION HD1 (NCT03761849), a Phase 3 study assessing tominersen, and using data from the Digital-HD observational study.
Methods: Active digital assessments of motor function in the dMP include: Speeded Tapping Test; Draw-a-Shape Test; Chorea Test; Balance Test; U-turn Test; and Walk Test.

Feature selection based on cross-sectional correlation, intra-class correlation coefficient, and longitudinal signal-to-noise ratio was performed using the longitudinal data from study participants in HD OLE and HD NHS. The top candidates were evaluated using the GENERATION HD1 participants for independent confirmation.
Results: Beyond the previously published preselected features, novel features per active test were identified that show favorable longitudinal properties while keeping good cross-sectional properties. In addition, we found that the sensitivity to change was higher than corresponding clinical scales at 17 months in HD Integrated Staging System (HD-ISS) Stage 2 patients.
Conclusions: The Roche HD dMP has been used to collect data on >1,000 patients with HD in nearly 100 countries for up to 2 years. Longitudinal analysis suggests that it provides valid, reliable and sensitive measures of disease progression in HD, including HD-ISS Stage 2.

48

Relationship between Biomarkers and Clinical Signs and Symptoms in Adult Manifest Huntington's Disease: A Cross-Sectional Analysis from Baseline GENERATION HD1

Jonas Dorn[1], David J Hawellek[1], Patricia Sanwald Ducray[1], Julian Zhou[2], Peter McColgan[3]

[1]Roche Pharmaceutical Research and Early Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland
[2]Roche Pharma Product Development China, Shanghai, China
[3]Roche Products Ltd, Welwyn Garden City, UK

Background: Identification of sensitive biological markers of pathology relating to clinical signs and symptoms of Huntington's disease (HD) is crucial for effective HD therapy development.
Objective: Use the unprecedented breadth of data from the Phase 3 GENERATION HD1 (NCT03761849) study of tominersen to assess the relationship between imaging/fluid biomarkers and clinical/digital endpoints in manifest HD.
Methods: Baseline data from 791 participants of GENERATION HD1 with manifest HD, aged 25–65 years, with a diagnostic confidence level of 4, independence scale ≥70, and CAG-age product score >400, were analyzed. Clinical data included measures from the Unified HD Rating Scale (UHDRS) and assessments from the Roche HD digital monitoring platform. Imaging biomarkers included ventricular, caudate, and whole-brain boundary shift integral. Fluid biomarkers included cerebrospinal fluid (CSF) mutant huntingtin protein (mHTT) and CSF neurofilament light protein (NfL).
Results: We observed convergent patterns of association between biomarker modalities and clinical outcomes, with the strongest associations present for

the volumetric imaging of the whole brain, caudate nucleus, and lateral ventricles. mHTT and NfL also showed consistent, albeit weaker, associations, similar to the digital measures, for which Draw-a-Shape Test–based features showed the strongest associations. The composite UHDRS and symbol digit modalities test showed the strongest relationships with biomarker data.
Conclusions: Results from GENERATION HD1 confirm robust patterns of association between volumetric imaging/fluid biomarkers and clinical endpoints, providing evidence for convergent patterns across digital measures. Measuring the impact of HD across different biomarker modalities may enable a stronger biomarker signature of HD, supporting future clinical trials.

49

Describing the Safety Profile of Tominersen Using Integrated Data from Across the Tominersen Clinical Development Program

Valerie Schlegel[1], Katia Navarre[1], Alessia Nicotra[2], Erik Deurell[3], Oleksandr Malyshko[4], Julian Zhou[5], Peter McColgan[2]

[1]F. Hoffmann-La Roche Ltd, Basel, Switzerland
[2]Roche Products Ltd, Welwyn Garden City, UK
[3]Genentech Inc, South San Francisco, CA, USA
[4]Intego Group LLC, Kyiv, Ukraine
[5]Roche Pharma Product Development China, Shanghai, China

Background: Tominersen is an intrathecally administered antisense oligonucleotide therapy designed to lower levels of huntingtin protein in the brain. Patients with manifest Huntington's disease have been treated in the Phase 2 (Open-Label Extension) and Phase 3 studies with different dosing regimens: 120 mg tominersen given once every 4, 8, or 16 weeks, or placebo.
Objective: Describe the safety profile of the different dosing regimens across the tominersen program by comparing the adverse event (AE) profile of different frequencies of intrathecal injections of 120 mg tominersen or placebo, including the lumbar puncture–related events, as well as cerebrospinal fluid (CSF) laboratory data and ventricular volume data.
Methods: The Roche database includes safety data from 767 patients treated with tominersen during a mean (standard deviation) duration of 471.3 (200.9) days (total patient-years at risk: 1,015.7).
Results: AEs per 100 patient-years will be presented by dosing regimen. In addition, CSF safety laboratory data and ventricular volume data will be analyzed across the program.
Conclusions: The safety profile of 120 mg tominersen improves by decreasing the frequency of dosing. The overall AE profile of 120 mg tominersen every 16 weeks is comparable to that of placebo.

50

How Can Clinical Trials and Outreach Contribute to Engagement of Prodromal and Early-Manifest HD Patients?

Joie Hucko, Robin Kuprewicz, Richa Kuklani, Karen Anderson

MedStar Georgetown University Hospital Huntington's Disease Research, Education, and Care Center, Department of Psychiatry and Department of Neurology, Georgetown University Medical Center, Washington, D.C., USA

Background: In May 2022, the Georgetown University's Huntington's Disease (HD) Center added an outreach coordinator (OC) to assess unmet needs of the community.
Objective: (1) Establish a baseline of prodromal and early-manifest HD patients seen at the center; and (2) collect data on the relationship of the OC and Enroll-HD participation and engaging this population who have not yet sought care for HD.
Methods: Using the Enroll-HD study, we compared data on how many prodromal and early-manifest HD participant study visits occurred prior to the OC starting to a one-month sample of Enroll-HD visits in summer 2022. We also utilized a survey to gather feedback regarding interest in HD research.
Results: The center averages around 70 Enroll-HD visits each year, with five new prodromal and early-manifest enrollments per year. From June 2022 to July 2022, the research team conducted 13 visits, accounting for 30% of visits so far in 2022, and doubled the prodromal and early-manifest enrollments for the year. The results of the survey over the same time period showed that 70% of respondents were interested in research and clinical care.
Conclusions: This project explores the role of clinical trials, community outreach, and support opportunities in serving the prodromal and early-manifest

HD community in and around Washington, D.C. We project that we will increase engagement by 50% over 2 years with this population and the center, fulfilling an unmet need in the HD community.

51

Elevated GFAP and UCHL-1 in Plasma and CSF in HD

Fiona C. Kinsella[1], Lauren M. Byrne[1], Filipe B. Rodrigues[1], Eileanor B. Johnson[1], Enrico De Vita[2,3,4], Daniel C. Alexander[5], Giuseppe Palermo[6], Rachael I. Scahill[1], Amanda Heslegrave[7,8], Henrik Zetterberg[7,8,9,10], Edward J. Wild[1]

[1]Huntington's Disease Centre, UCL Queen Square Institute of Neurology, University College London, London, UK
[2]Lysholm Department of Neuroradiology, National Hospital for Neurology and Neurosurgery, London, UK
[3]Neuroradiological Academic Unit, Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, University College London, London, UK
[4]Department of Biomedical Engineering, School of Biomedical Engineering and Imaging Sciences, King's College London, London, UK
[5]Centre for Medical Image Computing, Department of Computer Science, University College London, London, UK
[6]Neuroscience, Ophthalmology, and Rare Diseases, Roche Pharma Research and Early Development, Basel, Switzerland
[7]UK Dementia Research Institute at UCL, London, UK
[8]Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, University College London, London, UK
[9]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden
[10]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden

Background: Huntington's disease (HD) is a progressive and fatal neurodegenerative disorder. Studies have shown certain biofluid protein concentrations, such as mutant huntingtin (mHTT) and neurofilament light (NfL), can be used as disease progression markers and clinical trial endpoints. However, the abilities of other biofluid proteins are unknown.
Objective: Identify novel biofluid protein biomarkers for use in the field of HD.
Methods: Glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal-hydrolase L1 (UCHL-1) concentrations were assessed in CSF and plasma. These concentrations were then compared with clinical, cognitive, and neuroimaging measures as well as levels of CSF mHTT, CSF NfL, and plasma NfL in control, premanifest, and manifest participants.
Results: CSF GFAP, plasma GFAP, and CSF UCHL-1 were elevated in manifest participants. CSF GFAP was associated with total motor score (TMS), gray matter volume and CSF mHTT, CSF NfL, and plasma NfL. Plasma GFAP was associated with caudate volume reduction, CSF/plasma NfL, and the cumulative Unified HD Rating Scale (cUHDRS) as a whole and the TMS, total functional capacity (TFC), and Stroop Word Reading (SWR) individually. CSF UCHL-1 was associated with disease burden score (DBS), cUHDRS, TMS, TFC, symbol digit modalities test, SWR, verbal fluency-categorical test, CSF mHTT, and CSF/plasma NfL. Plasma UCHL-1 was associated with DBS and gray matter volume.
Conclusions: Biofluid biomarkers play an important role in designing and conducting clinical trials as well as furthering our understanding of HD neuropathology. Currently, CSF UCHL-1 and plasma GFAP may offer more insight into HD as disease state or monitoring biomarkers operating in parallel with established biomarkers.

52

Improving Access to Care: Educating Community-Based Genetic Counselors about HD

Deb Lovecky,[1] Meghan Carey[2], Katie Strang[2], Tanya Bardakjian[3], Matt Bower[4], Sandra Kostyk[5], Arik Johnson[6], Mara Sifry Platt[7], Ami Rosen[8], George Yohrling[1]

[1]Huntington's Disease Society of America, New York, NY, USA
[2]National Society of Genetic Counselors, Chicago, IL, USA
[3]University of Pennsylvania, Philadelphia, PA, USA
[4]University of Minnesota, Minneapolis, MN, USA
[5]Ohio State University, Columbus, OH, USA
[6]University of California, Los Angeles, CA, USA
[7]Kaiser Permanente, Roseville, CA, USA
[8]Emory University, Atlanta, GA, USA

Background: Huntington's disease is rare, and thus there are a limited number of trained, qualified genetic counselors across the United States able to provide supportive genetic testing and counseling.

While the Huntington's Disease Society of America (HDSA) has strategically positioned 55 HDSA Centers of Excellence (plus ten partner sites), across the United States, many HD families are unable to or elect not to use one within their region. Thus, many at-risk individuals may not receive genetic counseling, an integral part of a positive testing experience, and may be given their test results, often by telephone, with little explanation of what their test result may mean.

Though currently only about 10% of those living at risk for HD elect to be tested annually, the prospect of disease-modifying treatments, and the launch of clinical trials to test these new treatments that require the individual to know their genetic status, could lead to many getting tested through a healthcare professional other than a qualified genetic counselor. In anticipation of a rush to be tested to qualify for these clinical trials and eventually treatment options, HDSA identified a need to educate community-based genetic counselors about Huntington's disease in order to address this unmet need for that segment of the HD community that receives care outside of the HDSA Centers of Excellence network.
Methods: In 2019, HDSA joined with the National Society of Genetic Counselors (NSGC) to create a free multimodule accredited continuing education (CE) course for genetic counselors and genetic counseling students that is hosted on the NSGC website. The goal was to increase access to HD-knowledgeable community-based genetic counselors to ensure that at-risk individuals could receive a positive testing experience, whether they went to an HDSA Center of Excellence or their local genetic counselor. Experts from HDSA Centers of Excellence were tapped for both program development and as presenters.
Results: The five-part course launched in April 2020 with a goal to educate and award CE units to 600 genetic counselors within 3 years. Within 19 months of launch, 625 genetic counselors/students had successfully completed the course.
Conclusions: Partnering with a nationally recognized professional association such as the National Society of Genetic Counselors has allowed HDSA access to educate hundreds of community-based genetic counselors and genetic counseling students across the US. Providing the expert knowledge, tools, and ongoing resources these professionals need when they need them remains key to ensuring quality care for all persons affected by HD. Offering free CEs, which are required for licensing, ensures that the maximum number of professionals are exposed to the course and the information provided.

53

Long-Term Care for HD in South Carolina

Melissa Reitmeier[1], Miroslav Cuturic[2], Ala Bengal[1], Evelyn Morgan[1], Troy Boone[3], Ruth Abramson[2]

[1]University of South Carolina College of Social Work, Columbia, SC, USA
[2]University of South Carolina School of Medicine, Columbia, SC, USA
[3]Prisma Health Research, Columbia, SC, USA

Background: Placement of Huntington's disease (HD) patients to long-term care facilities has been extremely challenging in South Carolina.
Objective: To identify interest and requirements in long-term care facilities for HD patients.
Methods: We sent a written survey to all South Carolina long-term care facilities, including nursing homes, with our ongoing offer to provide HD education and assistance. The survey inquired about admissions policies, beds availability, cost, acceptance, and exclusion criteria for admission. The survey also asked about prior exposure to HD patients, experience, and knowledge about HD, as well as interest in receiving pertinent training.
Results: Thirty-two centers (16%) responded, citing basic cost/month ranging from $2,000 to ≥$7,000, with Medicaid accepted in 28% of centers. Entry criteria included fulfillment of the state requirements for assisted living, secured service payment, and certification by a physician and medical record. Patient behavior evaluation (n=4) and case-by-case review (n=3) were also cited. Exclusion criteria for 72% of facilities included violent/aggressive behavior and criminal/sexual offender conviction.

Sixty-nine percent of respondents had never worked with an HD patient. Centers that had experience with HD cited fall risk, motor symptoms, and behavior problems as main issues. Finally, 31% of responders indicated interest in an in-person or virtual training, while 16% deferred decision to corporate management.
Conclusions: We identified a definite need for increased advocacy, communication, education, and training within the long-term care facilities pertaining to HD.

54

Estimation of Health State Utilities in Huntington's Disease: A Targeted Review

Jennifer Petrillo[1], Kyle Paret[2], Ruta Sawant[1], Aaron Koenig[1], Sorrel Wolowacz[2], Naoko Ronquest[2], Hugh Rickards[3]

[1]*Sage Therapeutics, Inc., Cambridge, MA, USA*
[2]*RTI Health Solutions, Research Triangle Park, NC, USA*
[3]*University of Birmingham, Birmingham, United Kingdom*

Background: Quantifying the impact of Huntington's disease (HD) on patients' health related quality of life (QoL) is critical to evaluating the disease burden and potential value of new therapeutics. This is often done by estimating health state utilities (HSU), which reflect preferences for various health states.
Objective: To evaluate and summarize types of HSU measures used in HD.
Methods: A targeted literature review of utility studies in HD was conducted in PubMed.
Results: Seven studies were identified across the United States and Europe. The most common generic HSU measures used included EQ-5D (N=5) and SF-6D (N=2). Utility estimates decreased with increasing HD severity within studies; however, there was significant variation across studies. EQ-5D reported: mild/prodromal [0.89–0.79], moderate [0.80–0.39], severe/late-stage [0.71–0.11]. The SF-6D showed similar trends, but overall estimates were close to those for the age-adjusted normal general population. One study valued health state descriptions (vignettes) for chorea severity stages only while maintaining the same level of overall HD severity.
Conclusions: This review identified very large ranges and overall uncertainty in existing utility estimates in HD. There is some evidence that SF-6D is less sensitive than EQ-5D, and there is large variability in EQ-5D estimates resulting in substantial uncertainty. While different symptoms in HD (cognitive/motor/behavioral) all have varied effects on QoL and may be differentially affected by new treatments, very limited evidence was found for symptom-specific utilities. Further research is needed to reliably measure preferences and valuation in all stages and symptom clusters of HD, to inform decision-making for new treatments.

55

Assessing Psychometric Properties of the Huntington's Disease (HD) Everyday Functioning (Hi-DEF) using Rasch Measurement Theory

Jennifer Petrillo[1], Emma Elliott[2], Rebecca Rogers[2], Sophie Cleanthous[2], Ruta Sawant[1], Flora Mazerolle[2], Aviva Gillman[2], Stefan Cano[2], Sarah Baradaran[1], Rajeev Kumar[3], Jennifer Klapper[4], Luis A. Sierra[5], Jee Bang[6], Karen Elta Anderson[7], Deborah Hall[8], Susan Perlman[9], Henry Moore[10], Danny Bega[11], Aaron Koenig[1], and Jason Johannesen[1]

[1]*Sage Therapeutics, Inc., Cambridge, MA, USA*
[2]*Modus Outcomes, a Division of THREAD, Cambridge, MA, USA*
[3]*Rocky Mountain Movement Disorders, Englewood, CO, USA*
[4]*University of Pennsylvania Huntington's Disease Center, Philadelphia, PA, USA*
[5]*Beth Israel Deaconess Medical Center, Boston, MA, USA*
[6]*Johns Hopkins Medicine, Baltimore, MD, USA*
[7]*Georgetown University, Washington, DC, USA*
[8]*Rush University, Chicago, IL, USA*
[9]*University of California, Los Angeles, CA, USA*
[10]*University of Miami, Miami, FL, USA*
[11]*Northwestern Medicine, Chicago, IL, USA*

Background: The Huntington's Disease (HD) Everyday Functioning (Hi-DEF) scale is a new patient-reported outcome measure, developed with patient and care provider input, to assess the impact of higher-order cognitive impairment on daily functioning.
Objectives: To assess the psychometric properties and finalize the content of the Hi-DEF using Rasch Measurement Theory (RMT) analyses.
Methods: A cross-sectional, non-interventional validation study conducted across nine HD centers of excellence in the US. Participants had confirmed HD diagnosis; positive *HTT* gene-mutation (CAG repeats ≥36); 25–65 years; and Unified Huntington's Disease Rating Scale total functional capacity score 8–13. The Hi-DEF and other measures were administered remotely (further details can be found in REG-0060 and elsewhere).
Results: The study included 151 patients with HD: mean age = 47±12 years; 59% female; and 52% working full/part-time. RMT analyses reduced the Hi-DEF by 7 items (n=5 statistical dependence/con-

ceptual overlap; n=2 due to fit issues/disordering of response options). The final item-set (40 items) produced good reliability (person separation index 0.92/72% sample coverage). In terms of response options, 73% of items displayed ordered thresholds, indicating the response options measure distinct categories. Minimal statistical misfit (1 item) and dependency (3% of item pairs) were observed, and no differential item functioning (DIF) was found across age and sex.

Conclusions: RMT methods established an optimal set of 40 items representing tasks of everyday function in four domains (home, work, driving, communicating). Psychometric evaluation confirmed good reliability, targeting, and response ordering. Classical Test Theory analyses of reliability and validity are described in REG-0060.

56

Reliability and Construct Validity of the Huntington's Disease (HD) Everyday Functioning (Hi-DEF) Using Classical Test Theory Approach

Jennifer Petrillo[1], Emma Elliott[2], Rebecca Rogers[2], Sophie Cleanthous[2], Ruta Sawant[1], Flora Mazerolle[2], Aviva Gillman[2], Stefan Cano[2], Sarah Baradaran[1], Rajeev Kumar[3], Jennifer Klapper[4], Luis A. Sierra[5], Jee Bang[6], Karen Elta Anderson[7], Deborah Hall[8], Susan Perlman[9], Henry Moore[10], Danny Bega[11], Aaron Koenig[1], and Jason Johannesen[1]

[1]Sage Therapeutics, Inc., Cambridge, MA, USA
[2]Modus Outcomes, a Division of THREAD, Cambridge, MA, USA
[3]Rocky Mountain Movement Disorders, Englewood, CO, USA
[4]University of Pennsylvania Huntington's Disease Center, Philadelphia, PA, USA
[5]Beth Israel Deaconess Medical Center, Boston, MA, USA
[6]Johns Hopkins Medicine, Baltimore, MD, USA
[7]Georgetown University, Washington, DC, USA
[8]Rush University, Chicago, IL, USA
[9]University of California, Los Angeles, CA, USA
[10]University of Miami, Miami, FL, USA
[11]Northwestern Medicine, Chicago, IL, USA

Background: The Huntington's Disease (HD) Everyday Functioning (Hi-DEF) scale is a new patient-reported outcome (PRO) measure to assess the impact of higher-order cognitive impairment on daily functioning, consisting of 40 items over four subscales (home, work, driving, communicating).

Objectives: To assess the reliability and construct validity of the Hi-DEF scale using Classical Test Theory (CTT) analyses.

Methods: A cross-sectional, non-interventional validation study conducted across nine HD centers of excellence in the US (REG-0059). Validation measures included the Unified Huntington's Disease Rating Scale [UHDRS] total functional capacity [TFC], HD-PRO-TRIAD [HPT], and Cambridge Neuropsychological Test Automated Battery [CANTAB] measures (Emotional Recognition Task, One Touch Stocking of Cambridge, Paired Associated Learning, Spatial Working Memory, and Spatial Span). Psychometric properties assessed included: reliability (Cronbach's α), convergent validity, and known-groups validity as defined by TFC scores and CANTAB normative-referenced scores.

Results: The study included 151 patients with HD (REG-0059). Hi-DEF total/subscales showed good internal consistency reliability (α=0.87–0.98). Convergent validity was supported by moderate correlation with the UHDRS TFC (r_s=-0.54), high correlation with HPT total (r_s=0.90), moderate correlation with SWM (r_s=-0.38). Known-groups validity was supported; participants with TFC scores 8–10 scored significantly higher, indicating worse performance, on the Hi-DEF (39.0) than those with TFC 11–12 (35.4) or TFC 13 (20.8), $p<0.001$.

Conclusions: The 40-item Hi-DEF scale is a reliable and valid de novo PRO measure to assess the impact of higher-order cognitive impairment on daily functioning in patients with HD. Next steps include research to establish a meaningful change threshold in this target population.

57

The Effect of Food on Pharmacokinetics of PTC518, a Splicing Modifier and Potential Treatment for Huntington's Disease. Results of a Phase 1 Open-Label Crossover Study

Brian Beers, Rakesh Gollen, Diksha Kaushik, Lee Golden, Ronald Kong, Amy-Lee Bredlau, Kate L. Li, Rene Gallegos

PTC Therapeutics, Inc., South Plainfield, NJ, USA

Background: PTC518 is a splicing modifier that promotes the inclusion of a pseudoexon containing a premature stop codon (psiExon), leading to huntingtin (HTT) messenger RNA (mRNA) degradation and lowering of protein levels. The Phase 1 first-in-human study demonstrated that PTC518 was orally bioavailable and reduced HTT mRNA and total HTT protein in healthy volunteers (HV). Pharmacokinetic/pharmacodynamic analysis supports further evaluation in a Phase 2 trial for the treatment of Huntington's disease. Here we report the pharmacokinetics and the effect of food after a single oral dose of PTC518 in HV.
Objective: The primary objective was to characterize the effect of low-/high-fat meals on the pharmacokinetics of PTC518. The secondary objective was to characterize the safety and tolerability of a single dose of PTC518.
Methods: Twenty-four healthy adult male and female subjects participated in an open-label, 2-period, crossover design under three conditions: A–low-fat fed; B–high-fat fed; C–fasted. Subjects were allocated to 1 of 3 treatment blocks, then randomly assigned to 1 of 6 possible treatment sequences. The 3 treatment blocks included the following conditions tested in sequence (or reverse): A+B; A+C; B+C. Subjects received one 20 mg dose of PTC518 at the start of each treatment period with a 21-day washout between doses (≥8 PTC518 half-lives). Various pharmacokinetic parameters of PTC518 were evaluated for each treatment period. Safety assessments included treatment-emergent adverse events, clinical laboratory findings, vital signs, electrocardiogram, and physical exams.
Results: Results of the study will be available for presentation at the 2022 HSG annual meeting.

58

Relationship between Huntington's Disease Stage/Functional Capacity and Chorea Severity Using Enroll-HD Data: A Multiple Regression Analysis

Shoshana Reshef,[1] Erin Furr Stimming,[2] Victor Sung,[3] Rosa Willock,[4] Rinat Ribalov,[5] Jose Robles-Zurita,[4] Sam Leo[6]

[1]Teva Branded Pharmaceutical Products R&D, Inc., Epidemiology and Global Health Economics and Outcomes Research, Parsippany, NJ, USA
[2]UTHealth, McGovern Medical School, Houston, TX, USA
[3]University of Alabama at Birmingham, Birmingham, AL, USA
[4]HCD Economics Ltd, Cheshire, United Kingdom
[5]Teva Pharmaceutical Industries Ltd., Global Health Economics and Outcomes Research, Tel Aviv, Israel
[6]Teva Branded Pharmaceutical Products R&D, Inc., Global Health Economics and Outcomes Research, Parsippany, NJ, USA

Background: Huntington's disease (HD) progression is accompanied by decreases in total functional capacity (TFC). However, data on progression of HD-related chorea are limited. Analysis of data from Enroll-HD, a global, longitudinal, observational study, may elucidate the relationship between HD progression (per TFC) and chorea severity (per total maximal chorea [TMC] score).
Objective: To estimate the relationship between TFC and TMC.
Methods: Enroll-HD participants (aged ≥18 years; data cut 2013–2020) with manifest HD were grouped by baseline TFC scores (11–13/stage 1, 7–10/stage 2, 3–6/stage 3, 1–2/stage 4, and 0/stage 5) per Shoulson and Fahn staging. Baseline TMC scores were recorded as continuous variables (0 [least severe]–28 [most severe]). Change in baseline TMC score, given baseline TFC stage, was estimated with multiple linear regression (with stepwise inclusion of age, sex, presence of depression, and use of vesicular monoamine transporter 2 inhibitors, antipsychotic agents, and antidepressant agents).
Results: At baseline, mean TMC score for the group with greatest functional capacity (TFC=11–13) was 5.8. Estimated additive increases in TMC score from the TFC=11–13 reference group were 2.0 for TFC=7–10, 3.4 for TFC=3–6, 3.5 for TFC=1–2, and 3.5 for TFC=0. As TFC scores worsened, TMC scores worsened up to TFC=3–6, but did not increase further for TFC≤2. Stepwise inclusion of predictor variables did not change this relationship substantially.
Conclusions: Chorea severity increased as HD progressed (per TFC). However, beyond TFC=3–6/stage 3, chorea persisted but did not worsen, consistent with published observations.

59

Functional Rating Scale 2.0 (FuRST 2.0): Pilot Data for a Functional Patient-Reported Outcome in HD

Neha Sinha[1], Matthew Roche[1], Pua Feigenbaum[1], Rebecca L. M. Fuller[1], Nancy LaPelle[2], Swati Sathe[1], Prachi Dalal[1], Kelsey Johnson[1], Cristina Sampaio[1], Glenn T. Stebbins[3]

[1]CHDI Management/CHDI Foundation, New York, NY, USA
[2]Qualitative Research and Evaluation Consulting
[3]Rush University Medical Center, Chicago, IL

Background: As clinical trials move earlier in the course of Huntington's disease (HD) progression, sensitive endpoint measures are needed. The FuRST 2.0 is a patient-reported outcome (PRO) designed to be sensitive to HD's initial functional changes, since the current functional assessments are not. Its development followed standard methodology of focus groups, Delphi panel, and cognitive pretesting. Informal advice from a regulatory agency was also received. The psychometric properties of this PRO will be evaluated in a series of studies, FOCUS-HD: Online, in-person, and longitudinal.
Objective: Develop and validate a PRO measure of function in HD.
Methods: As a pilot study, individuals with HD attending an annual conference were invited to complete the FuRST 2.0 and a health questionnaire online.
Results: There were 21 HD respondents (9 male), with a mean age of 46.5 years (13.3) and mean CAG length of 43 (4.0). On the health questionnaire, 62% reported motor complaints and 67% reported cognitive difficulties. On the FuRST 2.0, the most severely affected function was driving with 30% indicating they no longer do this activity. Moderate difficulties were reported by 20–30% of the respondents on functions involving social interactions, planning, and movement.
Conclusions: When developing PROs, pilot data is an important consistency check. FOCUS-HD Online is designed to facilitate large-scale data collection and an expedited evaluation of the FuRST 2.0. The results of this study suggest online data collection is feasible and the FuRST 2.0 shows sensitivity in HD across multiple functional domains.

60

Huntington's Disease Society of America (HDSA) Disability Program Impact

Allison Bartlett, HDSA, New York, NY, USA

Background: Huntington's disease (HD) is a physically, legally, and financially devastating disease that impacts individuals during their prime working years. Most individuals with HD require disability assistance because they must stop working. The disability process is incredibly complex, so many HD individuals struggle to get approved for or miss out on important disability benefits.

HDSA identified a need to educate healthcare providers, social workers, and the HD community at-large on the multifaceted disability process to help families access and get approved for benefits. They created the HDSA Disability Program to meet these needs.
Objective: Highlight the importance of the HDSA Disability Program and its impact to reduce the burden of accessing disability benefits for HD-affected families.
Methods: Tracked number of HDSA disability connections through emails, phone calls, and online requests with HD families, social workers, and others (doctors, lawyers, and non-HD connections), and tracked disability topic areas through specialized software. Sent surveys to HD families, social workers, and HDSA Centers of Excellence network for feedback on effectiveness of disability resources.
Results: Since June 2019, there have been 2,973 connections with HD family members, social workers, and other contacts, covering nine disability topic areas. Surveys revealed that HDSA disability resources are incredibly effective, families and social workers rated resources 9/10, Centers of Excellence rated resources 8/10, and 52% of families indicated a reduced disability application timeframe.
Conclusions: The HDSA Disability Program is a highly used, impactful program that is improving the lives of HD families and reducing the application processing time for disability benefits.

61

Energy Expenditure, Fatigue, and Gait Impairments in Huntington's Disease

Ashwini K. Rao, Simone Norris, Paula Wasserman, Jacqueline Montes, Hiral Shah, Karen Marder

Columbia University, New York, NY, USA

Background: Huntington's disease (HD) is characterized by reduced aerobic capacity that begins in the prodromal phase. It is unclear if reduced aerobic capacity due to excess energy expenditure leads to fatigue.
Objectives: Examine energy expenditure, fatigue, and gait impairments during submaximal exercise in prodromal, manifest HD, and matched controls.
Methods: Ten manifest HD and 10 prodromal HD were recruited following genetic confirmation of HD and absence of acute medical illness. Ten controls were matched for age, sex, and body mass index (BMI). We collected energy expenditure and gait data during the six-minute walk test (6MWT) with a wearable accelerometer system, and assessed disease burden with the Unified Huntington's Disease Rating Scale (UHDRS). Outcomes included distance walked in 6 minutes (measure of weakness), decrement in distance from minute 1 to minute 6 (measure of fatigue), energy expenditure (EE), and gait markers (speed, stride length, cadence, and gait variability).
Results: All groups were well matched for age, sex, and BMI ($p > 0.05$). Total distance walked was reduced in manifest HD ($p<0.05$). Decrement in distance during the 6MWT was seen in prodromal ($p<0.02$) and manifest HD ($p<0.01$). Prodromal ($p<0.001$) and manifest HD ($p<0.002$) groups demonstrated higher EE compared with controls, despite lower gait speed and stride length at the end of the 6MWT. Gait variability was higher in prodromal and manifest HD groups compared with controls. 6MWT distance and decrement were correlated with UHDRS motor, cognitive, and functional scales.
Conclusions: Fatigue is seen in prodromal HD and is accompanied by weakness in early manifest HD. Prodromal and manifest HD demonstrated higher EE during the 6MWT despite walking at a slower speed and shorter stride length. Quality of gait was seen to deteriorate with fatigue in prodromal and manifest HD. Our results highlight the 6MWT as a good clinical measure of submaximal exercise capacity and fatigue.

62

Cortical Control of Balance and Gait in Huntington's Disease

Nicollette L. Purcell, Deborah A. Hall, and Joan A. O'Keefe

Rush University Medical Center, Chicago, IL, USA

Background: The ability to successfully multitask allows individuals to communicate and respond to environmental stimuli while navigating their environment. Individuals with Huntington's disease (HD) have difficulty with these processes and previously automatic tasks may require more attentional resources to maintain mobility and prevent falls. Our understanding of the neural mechanisms underlying the relationship between impaired cognition and balance and gait in HD is minimal. Portable functional near-infrared spectroscopy (fNIRS) provides a non-invasive means to functionally image the brain under ecologically valid conditions.
Objective: To examine the cortical control of balance and gait in HD under single-task (ST) and dual-task (DT) conditions.
Methods: Fifteen HD participants and 19 controls completed ST/DT balance and gait testing wearing inertial sensors and fNIRS to collect spatiotemporal gait and balance variables with concurrent prefrontal (PFC) and posterior parietal (PPC) cortical activity monitoring.
Results: Individuals with HD have greater PFC activation during ST walking vs. controls and greater PFC activation during ST vs. DT walking. The HD group exhibited greater PFC activation under DT vs. ST sway. Neuronal dysfunction resulted in HD individuals being unable to increase PPC activation during DT balance conditions to the same extent as controls.
Conclusions: More attentional resources are needed in HD during ST gait due to decreased gait automaticity. However, limited cognitive resources prevent HD individuals from further increasing PFC activity under DT gait. ST balance conditions may not demand the same PFC recruitment as ST gait; thus, PFC activation can further increase in HD when balance is challenged with a cognitive DT.

63

Enroll-HD Clinical Trial Committee

Tim McLean[1], Jenny Townhill[1,2], Juliana Bronzova[1], Cristina Sampaio[3], Swati Sathe[3] on behalf of the Enroll-HD Clinical Trial Committee

[1]European Huntington's Disease Network
[2]Cardiff University, Cardiff, UK
[3]CHDI Foundation, New York, NY, USA

Background: The Enroll-HD Clinical Trial Committee (CTC) is the entry point for industry and academic sponsors seeking provision of high-quality clinical advice and guidance, and/ or access to Enroll-HD platform operational support for conducting interventional therapeutic trials in Huntington's disease (HD). The CTC has so far provided advice and support to multiple small biotech and major pharmaceutical company partners working in HD.

The CTC comprises an operational management team and an independent advisory panel composed of HD expert clinicians and scientists, neurology clinical trial experts, and statisticians. The three main remits of the committee are: (i) provision of advice on protocol design and clinical development topics with access to experts from within the CHDI Clinical Department (including imaging, biomarkers, clinical outcomes, and disease modeling) and/or independent HD experts from the CTC advisory panel; (ii) review of final protocols for acceptance to allow access to the Enroll-HD platform operational support (e.g., in-silico feasibility, site identification, recruitment support (see Enroll-HD Platform Support poster for details); (iii) oversight and management of the HD Clinical Trial Site Certification Program open to Enroll-HD and non-Enroll-HD sites with capabilities and expertise to conduct HD clinical trials.

64

Salivary Huntingtin Protein: An Overlooked Biomarker for the Prognosis and Monitoring of Huntington's Disease

Georgia M Parkin[1,3], Jody Corey-Bloom[2], Chase Snell[2], Andrew Hall[2], Anna Smirnova[2], Braden Culbert[2], Emma Churchill[2], Elizabeth A. Thomas[1,3]

[1]Department of Epidemiology, University of California Irvine, Irvine, CA, USA
[2]Department of Neurosciences, University of California San Diego, San Diego, CA, USA
[3]Institute for Interdisciplinary Salivary Bioscience Research, University of California Irvine, Irvine, CA, USA

Background: The identification of biomarkers for Huntington's disease (HD) is critical for predicting symptom onset, monitoring disease progression, and tracking potential therapeutic interventions. Measuring peripheral huntingtin (Htt) protein represents an essential step in biomarker discovery for HD; however, to date, investigations into the salivary expression of Htt have been lacking.
Objective: To quantify total Htt (tHtt) and mutant Htt (mHtt) protein in matched plasma and saliva samples from HD patients and controls.
Methods: Total Htt was measured using the single molecule counting (SMC) 2B7-D7F7 immunoassay; mHtt was measured using the SMC 2B7-MW1 immunoassay. Matched plasma and saliva samples, and corresponding clinical data, were collected from 95 subjects: HD patients (n=19), premanifest HD (PM) individuals (n=34), and normal controls (NC) (n=42).
Results: Neither tHt nor mHtt levels were correlated in saliva and plasma. Plasma tHtt was significantly correlated with age (r=0.29, p=0.005) and participant sex (U=723, p=0.005), whereas salivary mHtt was significantly correlated with age (r=-0.27, *p*=0.01), CAG repeat number (r=0.33, p=0.02), and CAG age product (CAP) score (r=0.34, p=0.01). Cohorts did not differ in plasma or salivary tHtt levels. Both plasma and salivary mHtt levels were significantly increased in PM compared to NC; salivary mHtt was also significantly increased in HD compared to NC. There were significant correlations between a number of clinical measures, including total motor score and chorea, and salivary, but not plasma, tHtt and mHtt.
Conclusions: Salivary tHtt and mHtt offer substantial promise as relevant, noninvasive biomarkers for HD, and could be employed in both translational and clinical research applications.

65

Prediction of Caudate and Putamen Volume in Early Huntington's Disease Using Clinical Characteristics

Matthew J. Barrett[1], Nitai Mukhopadhyay[2], Jin Kim[3], Huma Nawaz[1], Jefin Jose[4], Claudia Testa[5]

[1]Department of Neurology, Virginia Commonwealth University, Richmond, VA, USA
[2]Department of Biostatistics, Virginia Commonwealth University Health, Richmond, VA, USA
[3]Virginia Commonwealth University School of Medicine, Richmond, VA, USA
[4]Virginia Commonwealth University, Richmond, VA, USA
[5]Department of Neurology, University of North Carolina School of Medicine, Chapel Hill, NC, USA

Background: Directly administering therapies into striatum in Huntington's disease (HD) patients requires sufficient striatal volumes. Volumetric magnetic resonance imaging (MRI) is rarely done clinically, and not available in some research cohorts, such as Enroll-HD.
Objective: The objective of this study was to determine if easily obtainable clinical variables can be used to predict caudate and putamen volumes.
Methods: We analyzed data from 1,374 IMAGE-HD, PREDICT-HD, and TRACK-HD participants. We imputed missing data for clinical variables with >72% non-missing values. A random forest algorithm was applied to build a predictive model for putamen volume >2,500 mm^3 and caudate volume >2,000 mm^3. A second model using logistic regression retained predictors significant at $p<0.05$.
Results: The random forest model with 1,000 trees and minimal terminal node size of 5 resulted in 83% area AUC. A probability cutoff of 0.75 resulted in 5% false positive and 57.7% false negative rates. Ten predictors had the greatest variable importance: age; CAG repeat size; Unified Huntington's Disease Rating Scale (UHDRS) total motor score and diagnostic confidence level; Stroop scores; Trail Making Tests A and B; and symbol digit modalities test (SDMT-correct). The logistic regression model retaining age, CAG repeat size, and SDMT-correct had 85.1% AUC. A probability cutoff of 0.8 resulted in <5% false positive and 66.7% false negative rates.
Conclusions: Random forest or logistic regression models can identify HD patients with striatal volumes above relevant cutoffs with a low false positive rate and false negative rate near 60% using easily obtainable clinical data. Effective prescreening would accelerate clinical trial enrollment and uptake of any future clinical interventions before striatal volume loss.

66

Characteristics of Coping in Huntington's Disease Patients and Their Adolescent and Young Adult Offspring

Abigail L.B. Snow[1], Abagail E. Ciriegio[2], Kelly H. Watson[2], Cara S. Guthrie[2], Marissa C. Roth[2], Abigail E. Pine[2], Anna C. Pfalzer[1], Spencer Diehl[1], Elizabeth Huitz[1], Lisa Hale[1], Daniel O. Claassen[1], and Bruce E. Compas[2]

[1]Vanderbilt University Medical Center, Nashville, TN, USA
[2]Vanderbilt University, Nashville, TN, USA

Background: Families affected by Huntington's disease (HD) are vulnerable to unique stressors caused by disease burden, placing HD patients and at-risk offspring for heightened risk of psychopathology. Understanding the ways that patients and family members cope with HD stress is a priority and the focus of this study.
Objective: To examine associations of HD patients and at-risk offspring reports of primary control (e.g., problem solving and emotional expression) and secondary control (e.g., acceptance and cognitive reappraisal) coping strategies with their symptoms of depression and anxiety.
Methods: Eighty-two HD patients and 98 at-risk offspring (M age = 20.9, SD = 7.84 years) provided self-reports of HD stress and coping (Responses to Stress Questionnaire-Huntington's disease version), and symptoms of depression and anxiety (Patient Health Questionnaire-9, Generalized Anxiety Disorder-7, Youth Self Report, and Adult Self Report).
Results: Higher reported use of both primary control and secondary control coping techniques was associated with lower depressive ($r_{primary}$ = -.30, $r_{secondary}$ = -.63, $p < .01$) and anxiety symptoms ($r_{primary}$ = -.35, $r_{secondary}$ = -.56, $p < .01$) for patients, whereas only secondary control coping was related to lower depressive (r = -.40, $p < .01$) and anxiety symptoms (r = -.45, $p < .01$) for offspring.
Conclusions: Both HD patients and at-risk adolescents and young adults may benefit from using secondary control coping techniques in the face of HD-related stress. Additionally, patients may benefit

from using primary control coping when dealing with stress, as they may have more control over their own medical care, participation in clinical trials, or symptom management in the early days of disease progression. These findings extend those of previous research and point to important avenues for intervention in families affected by HD.

67

Flamingo: A Retrospective Review of Single Limb Stance Time in a Huntington's Disease Clinic Population

D. A. Kegelmeyer[1], S.K. Kostyk[2], R. Minarsch[1], S. Ciolek[1], A. Kozich[1], K. Marita[1], A.D. Kloos[1]

[1]*Physical Therapy Division School of Health and Rehabilitation Sciences, The Ohio State University, Columbus, OH, USA*
[2]*Division of Neurology, Ohio State Wexner Medical Center, Columbus, OH, USA*

Background: Balance impairments such as increased postural sway, increased base of support, and gait alterations worsen over the course of Huntington's disease (HD), contributing to functional decline. Single limb stance time (SLST) using a cut-off of ≤10 seconds is a straightforward method of examining balance that has been used in older adults to assess balance impairment. Single-leg standing is of critical functional significance in activities such as turning, dressing, and stair climbing.
Objective: The present study objective was to assess how SLST correlated over time with HD progression in preparation for a prospective study of SLST and other balance and motor assessments in people with HD recruited from our HD clinic.
Methods: We retroactively reviewed charts of individuals seen in HD clinic between January 1, 2015, and July 1, 2022. Data from individuals who had undergone physical therapy assessments that included SLST were collated.
Results: We reviewed the records of 27 unique individuals who provided 94 data points. The mean number of clinic visits was 3.4. All but one of the participants could not do SLS of 10 seconds at 6 years (mean 6.37) from first reported symptoms. Over 75% of the time when SLS was ≤10 seconds the total functional capacity was >8 (mean 8.22). Sixteen individuals were unable to do SLS >10 seconds prior to 6 years from first onset of symptoms.
Conclusions: SLST is an important element of balance that correlates with fall risk and appears to be severely impaired early in the disease process in HD.

68

PIVOT-HD: A Phase 2, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of PTC518 in Subjects with Huntington's Disease

Brian Beers, Amy-Lee Bredlau, Anu Bhattacharyya, Allan Kristensen, Lee Golden, Matthew Klein, Stuart Peltz

PTC Therapeutics, Inc., South Plainfield, NJ, USA

Background: Huntington's disease (HD) is caused by expansion of cytosine-adenine-guanine (CAG) trinucleotide repeats in the huntingtin gene (*HTT*). The mutant protein is ubiquitously expressed and drives HD pathogenesis through a toxic gain-of-function mechanism. Animal models demonstrate that reducing huntingtin protein (HTT) levels alleviates HD symptoms. PTC518 is a splicing modifier that promotes the inclusion of a pseudoexon containing a premature stop codon (psiExon), leading to *HTT* messenger RNA degradation and lowering of HTT levels. Results of a Phase 1 trial demonstrated PTC518's ability to lower HTT in healthy volunteers, supporting Phase 2 evaluation.
Objective: The goal of the randomized, placebo-controlled, dose-ranging PIVOT-HD study (NCT05358717) is to evaluate safety, pharmacology, and biomarker effects of PTC518 in subjects with HD.
Methods: Approximately 162 subjects ≥25 years, with genetically confirmed HD (42–50 CAG repeats, inclusive), Unified HD Rating Scale (UHDRS)-independence scale score of 100, UHDRS total functional capacity score of 13, and a score of 0.18–4.93 inclusive on the normed HD prognostic index (PIN_{HD}) will be enrolled. Primary outcome measures: number of participants with adverse events through day 113 and change from baseline in blood total HTT at day 85. The effects of PTC518 on blood and cerebrospinal fluid biomarkers will also be observed. Participants will be randomized 1:1 to Part A (5 mg PTC518 once daily [QD]) or Part B (10 mg PTC518 QD) and then randomized within each Part 2:1 to PTC518 or placebo.

Based on the findings of Parts A and B, a third dose level may be studied.

69

Evaluating Health Cost Burden in HD Individuals and HD Companions: Implications of the Pandemic

Victoria Zolfaghari, Prachi Dalal, Sarah Weingast, Jamie Hamilton, Rebecca Fuller, Swati Sathe, Cristina Sampaio

CHDI Management/CHDI Foundation

Background: Previous research on the burden of Huntington's disease (HD) primarily focused on the impact on quality of life (QOL) for people with HD (PwHD) and HD companions; however, there is little research on the true costs associated with the burden of HD, particularly because of the COVID-19 pandemic.
Objective: The purpose of this study is to understand the pandemic impact on out-of-pocket costs for PwHD and HD companions within a community sample.
Methods: A brief online survey was distributed to Huntington's Disease Society of America 2022 conference attendees, aged 18 years and older. Respondents self-identified as English-speaking and were either PwHD or HD companions. Descriptive qualitative and quantitative data were collected.
Results: Of the 25 individuals enrolled, there were 7 PwHD and 18 HD companions. All respondents endorsed experiencing financial burden, with level of worry managing HD-related care costs being 1.27 times higher in HD companions than PwHD. Seventy-five percent of PwHD and 72% of HD companions were paying out-of-pocket for HD-related medical expenses, with 89% of HD companions not receiving any financial support. When managing care during the pandemic, 71% of PwHD felt their level of care received did not change, and 72% of HD companions felt their care responsibilities did not change.
Conclusions: Evaluating out-of-pocket cost burden and pandemic impact on a community-based sample of PwHD and HD companions provided a unique opportunity to examine health-related cost burden considerations. Financial burden is a source of concern for both PwHD and HD companions. Future work will explore these concerns in more detail.

70

The Role and Outcome of Dual-Task Interference on Balance in Prodromal and Manifest Huntington's Disease

Emma Churchill[1], Jody Corey-Bloom[2], Andrew Hall[2], Chase Snell[2], Anna Smirnova[2], Shelby Hughes[3], Braden Culbert[2], Lauren Bohall[2], Paul E. Gilbert[1], Daniel J Goble[4]

[1]Department of Psychology, San Diego State University, San Diego, CA, USA
[2]Department of Neurosciences, University of California San Diego, La Jolla, CA, USA
[3]San Diego State University/UC San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA
[4]Department of Exercise and Nutritional Sciences, Oakland University, Rochester, MI, USA

Objective: To investigate whether a cognitive-motor dual task (DT) paradigm uncovers deficits in balance in Huntington's disease (HD) and, more importantly, prodromal HD, compared to healthy adults (HA).
Background: Adding a simultaneous cognitive task to a balance assessment (referred to as dual task [DT] paradigm) may negatively impact motor performance—expressed in terms of a dual task cost (DTC).
Methods: Balance under single task (ST) and DT conditions was examined using the BTrackS balance plate and software in 30 HD, 11 prodromal HD (pro-HD), and 25 healthy adults (HA). During the DT condition, participants were simultaneously administered the Paced Auditory Serial Addition Test (PASAT). DTC, measured as a percent worsening, is calculated as the relative ratio of ST to DT, controlling for ST performance: DTC= (ST − DT)/ST x 100.
Results: Eyes-open DTC at 10 sec was minimal (2.80%) for the HA individuals, whereas individuals with HD showed 62.78% ($p<.001$) worsening and more importantly, pro-HD individuals showed 40.42% ($p=.004$) worsening compared to HA when the concurrent cognitive task was administered. Eyes-open DTC at 20 sec was 17.67% for the HA, 43.81% ($p = .006$) for the pro-HD, and 63.78% ($p<.001$) for the HD groups.
Conclusions: Likely reflecting real life, our findings indicate that the addition of a simultaneous cogni-

tive task negatively impacts motor performance in HD. The so-called DTC may have additional value for estimating transition to manifest disease, appraising fall risk, or serving as a valid outcome measure in both observational and interventional HD trials.

71

Graphomotor Predictors of Motor and Functional Decline in Premanifest Huntington's Disease

Braden Culbert[1], Michael Caligiuri[2], Emma Churchill[1,3], Nikita Prasad[1], Chase Snell[1], Andrew Hall[1], Anna Smirnova[1], Brenton A. Wright[1], Jody Corey-Bloom[1]

[1]Department of Neurosciences, University of California San Diego, La Jolla, CA, USA
[2]Department of Psychiatry, University of California San Diego, La Jolla, CA, USA
[3]Department of Psychology, San Diego State University, San Diego, CA, USA

Background: Previous research has identified multiple clinical and imaging predictors associated with motor decline or the onset of manifest HD. In these studies, early motor markers of decline were largely obtained from the motor portion of the UHDRS (UHDRS-TMS). We reasoned that a quantitative graphomotor procedure would offer greater sensitivity and predictability than conventional motor assessments.
Objective: To examine whether baseline graphomotor (handwriting) kinematics predict motor and functional decline in patients with premanifest (PM) Huntington's disease (HD).
Method: Twenty-eight gene-positive PM subjects underwent cognitive, motor, and behavioral clinical assessments at intake and were followed for up to 5 years with graphomotor procedures completed at each visit. Graphomotor, demographic, and clinical data were entered into multivariate regression analyses to identify baseline factors accounting for variability in each of two outcomes: 1) worsening UHDRS-TMS and 2) decline in the composite UHDRS (cUHDRS) score.
Results: Our strongest model predicting motor (TMS) decline included baseline clinical and graphomotor variables from a sentence task, with an R^2 of 0.91 (p=0.002). The strongest model predicting functional (cUHDRS) decline included baseline clinical and graphomotor variables from a rapid circle-drawing task, with an R^2 of 0.90 (p=0.005). Predictive models based on clinical or cognitive variables alone accounted for less than 25% of the variability in outcome.
Conclusions: Adding graphomotor assessments to a baseline clinical battery increases the predictive utility for TMS change from 23 to 91% and for cUHDRS change from 20% to 90% in PM HD subjects.

72

Move to Improve Telehealth Program to Overcome Exercise Barriers for Individuals with Huntington's Disease

Anne Kloos,[1] Sandra Kostyk,[2] Raquel Minarsch,[1] Audrey Hoffmeister,[1] Tim Wohl,[1] Yevgeniya Gokun,[3] Deb Kegelmeyer[1]

[1]Physical Therapy Division, School of Health and Rehabilitation Sciences, The Ohio State University, Columbus, OH
[2]Department of Neurology, College of Medicine, The Ohio State University, Columbus, OH
[3]School of Biomedical Sciences-Biomedical Informatics, College of Medicine, The Ohio State University, Columbus, OH

Background: Balance and cognitive impairments in individuals with Huntington's disease (HD) negatively affect their mobility, thereby decreasing their quality of life. Exercise interventions that combine movement and music have demonstrated positive effects on mobility and cognition in neurologic populations. Many people with HD cannot engage in regular exercise due to various barriers such as limited class offerings and lack of accessibility. We developed a movement to music motor-cognitive training exercise program, called "Move to Improve," designed to enhance physical, cognitive, and psychosocial health.
Objective: This pilot study aims to determine if implementation of this 12-week program will 1) be feasible and safe when delivered via telehealth to individuals with HD and their care partners, and 2) induce changes in specific physical, cognitive, and psychosocial function measures.
Methods: Thirty dyads (i.e., person with HD and care partner) will be recruited. Prerecorded Move to Improve classes conducted by a dance instructor are accessible 24/7 via computer or tablet. Each twice-weekly 45-minute class starts with a warm up and advances through a series of exercises that become

progressively more challenging and complex. Outcome measures include functional and cognitive measures, quality of life and mood questionnaires, attendance/retention rates, and adverse events.
Results: To date we have enrolled five dyads; weekly phone calls have revealed that they are participating in the classes. Participants report that they can easily access the class.
Conclusions: The online movement to music exercise program, Move to Improve, may help to overcome barriers to accessing exercise for people with HD.

73

HDSA's HD Trialfinder: Expanding Awareness of Huntington's Disease Clinical Studies in North America

Kelly Andrew and Leora Fox

Huntington's Disease Society of America (HDSA), New York, NY, USA

Background: The Huntington's Disease Society of America (HDSA) created HD Trialfinder (www.hdtrialfinder.org) in 2015 as a resource to help people affected by Huntington's disease (HD) to explore opportunities to participate in clinical trials. Existing sources of information, like clinicaltrials.gov, can be overwhelming and outdated; HD Trialfinder is a curated and user-friendly resource focused on actively recruiting trials. The service, powered by Carebox (https://careboxhealth.com/), includes a website and call center staffed by trained navigators.
Objective: HDSA sought to explore HD Trialfinder usage data, collected since 2015. We examined numbers of new and returning users, geography, uptake around community education events, trial views, and more.
Methods: Data regarding site visits, call center activity, trials viewed, profile matching, and reported enrollments was collected by Carebox and provided in Microsoft Excel spreadsheet format to HDSA, where it was graphed and analyzed.
Results: As of June 2022, there are 7,166 individual profiles eligible for matching, and an average of 778 site views monthly in the first half of 2022. After initial uptake, usage has steadily increased since 2016 with an average rate of 82 new matching profiles added monthly. We examined usage by region, user activity, and self-reported study enrollments. Site visits decreased due to the COVID-19 pandemic and increased around major educational events or trial announcements.
Conclusions: HD Trialfinder usage and self-reported enrollments have increased over time. The service is widely used by the North American HD population, and trends suggest that it has driven awareness and potentially recruitment of HD clinical studies.

74

The Development of Haplotype-Specific *HTT* BAC Clones for Global Genetic Modeling Application in Huntington's Disease Research

Jenna Aquino, Nalini Potluri, Yuanyun Xie, Amber L. Southwell

Burnett School of Biomedical Sciences, College of Medicine, University of Central Florida, Orlando, FL, USA

Background: With the first nonselective HTT lowering clinical trial recently halted, there is increased interest in maintaining wildtype HTT function through allele-selective single nucleotide polymorphism (SNP) targeting. Population genetics has identified the most common *HTT* haplotypes associated with the HD mutation worldwide. Unfortunately, there are only two sets of mouse lines expressing the full-length human *HTT* gene, and their haplotypes do not represent most Huntington's disease (HD) patients.
Objective: To generate novel human *HTT* clones with the most common haplotypes found on HD and control chromosomes.
Methods: We evaluated fibroblast cell lines with unusually long CAG tracts, which are required to cause disease in mice, and used DNA from the identified donor for bacterial artificial chromosome (BAC) library construction. Libraries were screened with SNP-specific PCR to identify A1 and C1 clones. Next-generation sequencing (NGS) of isolated clones was performed and aligned to the *HTT* reference sequence. Ambiguous sequences are being resolved by PCR to achieve single base-pair accuracy.
Results: The donor cell line contains the ideal haplotype combination A1/C1 and CAG tract length of 180, which is sufficient to cause HD-like phenotypes in a mouse with single gene copy number. Two BAC

libraries were generated following partial digestion with BamHI (12.6x depth, 110 kb avg insert) or HindIII (5.6x depth, 170 kb avg insert). Two *HTT* gene-spanning clones upstream of the 5′ untranslated region (UTR) through to the stop codon were isolated. Clones were haplotype-validated through tagging-SNP PCR and CAG sizing. NGS left ambiguous intronic sites, which are being resolved through PCR.

Conclusions: In ongoing work, we are using PCR assessment to achieve a fully constructed reference sequence for each clone. Additionally, recombineering will be used to introduce polymorphisms from other common *HTT* haplotypes. These clones will be useful for HD model development and genetic therapeutic design and assessment.

75

Inhibition of Impulsive Actions in Huntington's Disease

Shuhei Shiino[1], Nelleke Van Wouwe[2], Daniel O. Claassen[1], Katherine E. McDonell[1]

[1]*Department of Neurology, Vanderbilt University Medical Center, Nashville, TN, USA*
[2]*Department of Neurological Surgery, University of Louisville, Louisville, KY, USA*

Background: Impulsivity is a common clinical feature of Huntington's disease (HD), but the underlying neural mechanisms of impulse control in HD remain unclear.

Objective: To investigate the temporal dynamics of inhibitory control in HD patients using an action conflict task.

Methods: Sixteen motor manifest HD patients and 17 healthy controls (HC) completed the Simon task, which instructs participants to respond to spatially lateralized stimuli with a left or right button press based on the stimulus color. When the location and color of the stimulus are conflicting, this leads to errors and slowed responses. We applied a distributional analytic model to differentiate between the activation of fast action impulses (impulse capture) and slower deliberate inhibition of these impulses (impulse suppression).

Results: On average, HD patients responded more slowly and with lower accuracy than healthy controls. HD patients exhibited a more robust conflict effect with a greater difference in reaction time on conflicting versus nonconflicting trials (HD: 64 ms; HC: 25 ms; motor conflict x group: RT, $F[1,29] = 17.00$, $p = 0.000$). Participants with HD made more fast, impulsive errors than HC, showing a significantly lower accuracy rate on trials with the fastest reaction times (HD: 0.78; HC: 0.92; $F[1,29] = 6.193$, $p = 0.019$). Impulse suppression was similar between groups ($F[1,29] = 0.14$, $p = 0.906$).

Conclusions: Our results indicate that patients with HD show a greater susceptibility to act erroneously with conflicting action impulses (impaired impulse capture) but preserved impulse suppression. Further research is needed to determine how these findings relate to behavioral symptoms.

76

Analysis of Huntington's Disease Caregiver Quality of Life Using the Enroll-HD Population

Emilyn Banfield[1], Syed. S. Hashmi[2], Natalia Pessoa Rocha[3], Erin Furr-Stimming[3], Myla Ashfaq[4], Leslie Dunnington[4]

[1]*National Human Genome Research Institute, Bethesda, MD, USA*
[2]*Department of Pediatrics, UT Health Science Center at Houston, Houston, TX, USA*
[3]*Department of Neurology, UT Health Science Center at Houston, Houston, TX, USA*
[4]*Division of Medical Genetics, UT Health Science Center at Houston, Houston, TX, USA*

Background: Huntington's disease (HD) is a neurodegenerative condition inherited in an autosomal dominant manner caused by a CAG triplet repeat expansion within the *HTT* gene. Thus, HD is unique among neurodegenerative disorders with a caregiver population often burdened by both the caregiver role and concern over transmission to at-risk relatives.

Objective: We aimed to characterize quality of life (QoL) among caregivers over time, assess the association over time between caregiver and patient QoL, and identify factors associated with caregiver QoL.

Methods: Caregiver QoL over time was measured using the Enroll-HD study population, an observational cohort with data collected from study sites across 20 countries. Self-reported QoL measures from 3,591 caregiver/patient dyads at the first/baseline Enroll-HD appointment, 192 dyads at the third annual appointment, and 49 dyads at the fifth annual appointment were assessed.

Results: We found that at baseline and the third visit, HD caregivers reported negative feelings regarding their caregiver role, their QoL, and how others behave toward their loved one. By the fifth visit, they reported improvement in QoL and social stresses related to caring for an HD patient. There were no demographic subgroups uniquely associated with QoL over time.
Conclusions: These results are consistent with previous HD caregiver QoL studies. The use of a large, diverse caregiver population means that our results are applicable to the international HD community in previously unfeasible ways. They also highlight the need for targeted caregiver intervention by practitioners, genetic counselors, and social workers at various points throughout HD progression.

77

Huntington's Disease Society of America's Youth Social Worker Program

MaryAnn Emerick

Huntington's Disease Society of America, New York, NY, USA

Background: HDSA's National Youth Alliance (NYA) continues to grow, and the need for youth-specific social work services is evident. With more than 100 social workers nationwide, HDSA's social worker network is an important resource for families impacted by HD/juvenile HD (JHD). In 2018, HDSA piloted the HDSA Youth Social Worker (YSW) program to expand services for youth and young adults impacted by HD/JHD. Each YSW brings years of experience working with this cohort.
Objectives: Develop a network of social workers specializing in providing services to youth/young adults impacted by HD/JHD. Evaluate the impact of support for youth/young adults impacted by HD/JHD. Support the need for youth/young adult–specific information, education, and support.
Methods: HDSA provides the YSWs training, education, support, and opportunities to best engage youth/young adults within the community. Youth/young adults and families are educated at HDSA events, NYA retreats, the HDSA annual convention, and social media platforms about the YSWs. HDSA tracks services through service reporting software showing the impact of support provided.
Results: HDSA YSWs provide direct services, but also participate in community and professional education, consult with HDSA Centers of Excellence, and participate in HDSA's virtual and in-person NYA events. In 2021, the YSWs recorded more than 100 hours dedicated to education on youth/young adult–specific topics, and an increase in direct service hours with program expansion and awareness.
Conclusions: HDSA YSW program is a growing resource and impactful program used by many within the larger community, dedicated to improving the lives of youth/young adults impacted by HD/JHD.

78

Mitochondrial DNA Depletion and Decreased Mitochondrial DNA Repair Activity in Huntington's Disease

M. Lopez-Llegus, S. Ayala-Peña

Department of Pharmacology and Toxicology, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico

Background: Impairment of mitochondrial DNA (mtDNA) integrity, including oxidative damage and mtDNA depletion, is a hallmark of Huntington's disease (HD). Loss of mtDNA integrity due to deficient repair has the potential to cause neurodegeneration.
Objectives: We aimed to determine if mtDNA damage and/or depletion correlates with disease progression using grade 1, 2, and 3 HD postmortem caudate nucleus (CN) and if mtDNA repair is deficient in HD mouse striatal cells.
Methods: Levels of mtDNA abundance, mtDNA damage, and mtDNA repair kinetics were assessed using quantitative PCR. Repair activity of the apurinic/apyrimidinic endonuclease 1 (APE1), the main endonuclease in the base excision repair pathway, was measured using a fluorometric assay.
Results: We observed a significant 15%, 49%, and 44% decrease in mtDNA abundance in grade 1, 2, and 3 CN, respectively, but no increase in oxidative mtDNA or nuclear DNA damage, compared with controls. Correlation analysis showed a negative linear relationship between mtDNA abundance and disease progression. Consistent with the postmortem data, mutant huntingtin Q111 cells showed decreased basal mtDNA depletion, but treatment with 80 μM 2,3-dimethoxy-1,4-naphthalenedione (DMNQ), a redox-recycling agent, did not induce further mtDNA loss. Consistent with a significant ~10% decrease in APE1 activity in grade 3 postmor-

tem brain, Q111 cells exhibited deficient repair of mtDNA damage after DMNQ treatment, but not wild-type mouse striatal cells, underscoring a role for the mitochondria and DNA repair in HD.
Conclusions: Repair of mtDNA damage is impaired in HD mouse striatal cells, and mtDNA depletion may contribute to neurodegeneration and disease progression.

79

First Estimate of Huntington's Disease Prevalence in Puerto Rico

Zoé M. Cruz Gil, Christian González Serrano, Jessica Maisonet Llanos, Génesis Vázquez, Jarelys López Delgado, Gimarie Irizarry, Amilkar Matos Moreno, Diamar Calderón and Sylvette Ayala Peña

Fundación Huntington Puerto Rico, San Juan, PR, USA

Background: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder that causes the progressive deterioration of motor, cognitive and personality functions. Worldwide, HD occurs in an estimated 3-7 per 100,000 people of European ancestry; however, in Puerto Rico the HD prevalence is unknown.
Objective: When the Fundación Huntington Puerto Rico (a nonprofit organization with the mission to improve the quality of life of people living with HD) was established in 2016, the HD community in Puerto Rico was invisible and underserved. The main objective of this study was to estimate HD prevalence in Puerto Rico.
Methods: To identify the families, we educated and advocated about HD in local newspapers, radio, and TV, and educated healthcare professionals to become knowledgeable in HD. We performed home visits and obtained the clinical and sociodemographic information from HD cases representing 28.2% of the municipalities (22 out of 78 municipalities).
Results: We identified through genetic testing or family history 99 persons with HD and >255 people at risk of developing HD. Adult-onset patients at early, middle, and advanced disease stages and three juvenile cases have been identified, and 31 family pedigrees created. Our data demonstrate no clusters of HD patients in Puerto Rico. Finally, we report an estimated prevalence of 2 (1.68) per 100,000 people affected by HD in Puerto Rico.
Conclusions: The prevalence of HD in Puerto Rico may be similar to that reported worldwide. However, it may be underestimated due to the limited number of municipalities examined so far.

80

Natural History of Huntington's Disease in a Cohort Followed Until the End of Life

Ryotaro Fukuda BS, OTR, MS[1]; Ferheen Abbasi BS, MS[1], Alexandra Duffy DO[1,2], Eleonora Napoli PhD[1,2] and Vicki Wheelock MD[1,2]

[1]UC Davis School of Medicine, Sacramento, CA, USA
[2]Department of Neurology and HDSA Center of Excellence at UC Davis, Sacramento, CA, USA

Background: Huntington's disease (HD) is an autosomal dominant degenerative neuropsychiatric disease leading to death in an estimated 15 –20 years. Prior studies of survival in individuals with HD have been roster- or population-based and lack details about genetics and late-stage clinical features.
Objective: To describe clinical and genetic characteristics of a cohort of patients prospectively followed until death at a single multidisciplinary HD clinic and to determine the relationship between CAGn and age at death.
Methods: Following institutional review board approval, a retrospective chart review was conducted at the HDSA Center of Excellence at UC Davis. Inclusion criteria comprised patients seen between 2007-2022 with clinically and genetically-confirmed HD for whom clinical data, age and cause of death were available in the electronic health record. Descriptive statistics are presented as mean ± SD for continuous variables and proportions for categorical variables. Statistical analysis was performed with GraphPad Prism 9.4.1.
Results: Among 518 patients with HD, 149 had died and 109 met the inclusion criteria. The mean age at diagnosis was 49.4 ± 15.5 (mean ± SD) years and mean CAGn (expanded allele) was 45.5 ± 8.8 repeats. Mean age at death was 60.9 ± 14.4 years and showed a strong inverse correlation with CAGn ($r = -0.8262$, $p < 0.0001$). Median survival time after onset was 15 years (95% CI, 13-16 years). The most common cause of death was advanced HD, followed by suicide and other causes. Most patients (61%) were receiving care at home at the time of death, and half were enrolled in hospice.
Conclusions: This series of 109 HD patients prospectively followed at a single HD multidisciplinary

care center until the end of life includes detailed genetic and clinical measures. Demographics and mean age at death were similar to other population-based studies. Age at death was inversely correlated with CAGn. Mean survival after symptom onset was shorter than in prior published European cohorts, possibly due to variability in identifying onset. The most common cause of death was advanced HD, followed by suicide. Additional clinical characteristics of late-stage HD and correlates of survival will be presented.

81

Dysregulated Endonuclease Activity of Human and Mouse Apurinic/ Apyrimidinic Endonuclease 1 Is Associated with Deficient Repair of Mitochondrial DNA in Huntington's Disease

María del Rocio Castro[1], María M. López-Llegus[1], Sol V. Pérez-Mártir[1], Jaime Pérez-Lizardi[1], Ashley M. Jiménez Valentín[1], Javier Rivera Hernández[1], Carlos A. Torres-Ramos[2], Cynthia T. McMurray[3], and Sylvette Ayala-Peña[1]

[1]*Department of Pharmacology and Toxicology, University of Puerto Rico Medical Sciences Campus, San Juan, PR, USA*
[2]*Department of Physiology, University of Puerto Rico Medical Sciences Campus, San Juan, PR, USA*
[3]*Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA, USA*

Background: Novel genetic analyses suggest that DNA repair is central in modifying the onset and progression of Huntington's disease (HD). The apurinic/apyrimidinic endonuclease 1 (APE1), the main endonuclease in the base excision repair pathway, is necessary for the efficient repair of oxidative DNA damage in neurons and with the maintenance of mitochondrial function in HD. However, whether APE1 repair function is impaired in HD is uncertain.
Objective: To test the hypothesis that mutant huntingtin may lead to reduced APE1 repair function and to increased levels of mtDNA damage.
Results: APE1 endonuclease activity is significantly reduced in human postmortem caudate brain tissue and in striatum and cerebral cortex of two mouse models of HD, the transgenic R6/2 and *HdhQ150* knock-in mice. A significant accumulation of mtDNA damage in both the caudate and the cerebral cortex tissues is consistent with APE1 limiting mtDNA repair in HD. In vitro studies using mouse striatal cells show that mutant huntingtin–expressing cells were deficient in repairing a second event of H_2O_2-induced mtDNA damage. A concomitant reduction in APE1 endonuclease activity was observed only in the mutant cells, indicative of reduced repair capacity. Generation of mitochondrial reactive oxygen species (ROS) with 2,3-dimethoxy-1,4-naphthoquinone (DMNQ) caused a rapid increase in mtDNA damage only in the mutant cells, which failed to repair the DMNQ-induced damage.
Conclusions: Our findings suggest that APE1 endonuclease activity is impaired in postmortem brains and in vivo and in vitro models of HD and that repair of mtDNA damage is deficient in mutant huntingtin–expressing mouse striatal cells.

82

Exploring Diabetes Incidence and Presentations and Diabetes Medications in Individuals with Huntington's Disease Using the Enroll-HD Database

Yuan Huang[1] and Sandra Kostyk[2]

[1]*Yale University, New Haven, CT, USA*
[2]*The Ohio State University, Columbus, OH, USA*

Background: Huntington's disease (HD) has widespread effects on metabolic function, particularly on glucose metabolism. Peroxisome proliferator-activated receptor *(*PPAR) gamma agonists and biguanides are used to treat type 2 diabetes (DM2) and have demonstrated survival and motor function benefits in HD mouse models.
Objective: To explore the incidence and presentation of DM2 in HD and identify DM2 medications usage for future analyses.
Methods: The Enroll-HD database was used to examine incidence and timing of diagnosis of HD and DM2, body mass index (BMI), and DM2 medication usage. The impact of DM2 on motor onset was explored through in-depth survival analysis on a subset of participants. Primary analysis used time of DCL conversion to 4 as motor onset and is based on the time-dependent Cox model accounting for left truncation.
Results: Data on 21,086 individuals were queried. Of 619 DM2 individuals, incidence of DM2 was significantly lower in HD. Age of DM2 diagnosis var-

ied with CAG size. Differences in BMI were observed between groups. Eight classes of diabetes medications were used by individuals with HD, with the majority using biguanides. Thirty-two HD individuals were identified using PPAR gamma agonists. Survival analysis reveals that DM2 has an adverse impact on HD onset [HR=1.59, 95% confidence interval (CI) = (1.08, 2.36)]. Separate analysis reveals that age of onset is affected more in males [HR=1.97, 95% CI = (1.11, 3.49)] than in females [HR=1.21, 95% CI = (0.67, 2.19)].

Conclusions: These observations emphasize factors, including CAG repeat size and BMI, to consider in understanding how metabolic processes may impact disease progression in clinical trials.

Journal of Huntington's Disease 11 (2022) S47–S55
DOI 10.3233/JHD229005
IOS Press

Author Index