Implementing De-Escalation Training to Nursing Staff Caring for Residents with Huntington’s Disease

Brandon Rogers*

University of Iowa Hospitals and Clinics, IA, USA

Background: Huntington’s disease (HD) is a rare, fatal genetic neurodegenerative disorder that affects 1 in every 10,000 people in the United States. Approximately 30,000 total have been diagnosed with HD, while close to 200,000 are at risk for developing HD at some point in their lifetime. HD is characterized by the manifestation of behavioral disturbances, cognitive decline, and motor disorder that develop over the lifetime of the disease. Those afflicted will eventually require 24-hour-a-day care at a long-term care facility. Caring for those with HD in long-term care facilities presents a number of challenges for the staff in long-term care settings.

Objectives: This project was designed to help provide non-physical de-escalation training to help staff work with residents who present challenging behaviors.

Methods: Participants selected were employees at a central Iowa long-term care facility. Employees consisted of nursing staff (registered nurses and certified nursing assistants), nursing administration, and auxiliary staff (maintenance, housekeeping, recreation therapy, kitchen, and laundry staff). “Safety Care” training days were established for the staff, and the training module was taught over the course of a day. In addition to the training, they also received a one-hour informational session about HD provided by the instructor of Safety. Staff were given a survey prior to the class and then re-assessed 30 days post education. A chart review of patient behaviors—including searching for the key terms: agitation, aggression, irritable, refused, as-needed medication, as-needed medication, “PRN” medication, yelling, hitting, throwing, spitting, and swearing—was conducted, and total behavioral incidences both pre- and post-Safety Care education were recorded.

Results: Survey results showed improvements in staff job satisfaction and confidence in caring for individuals with HD, as well as confidence in their coworkers’ abilities to work with residents with HD. Residents’ agitated behaviors and refusal behaviors (refusing meals, medications, and bathing) decreased post-Safety Care education.

Conclusions: Use of applied behavioral analysis-based training systems such as Safety Care may provide an adequate educational foundation for caring for individuals with HD and may provide staff with confidence in caring for the complex behaviors of HD.
Results: Overall, 418 patients met the HD algorithm definition; 23 patients were excluded from the BOI cohort (n=395). The mean [standard deviation] age at index date was 53.9 [13.8] years, and 53.7% were female. The most common comorbidities were depression (70.1%), dementia (49.4%), and dysphagia (44.3%). The five-year average annual HD incidence was 0.83 per 100,000 person-years, and the five-year period prevalence was 12.15 per 100,000. For HRU outcomes, substantial mean number of visits per person-year were observed for general practitioners (19.2 [18.8]) and specialist practitioners (12.2 [25.5]). The mean total all-cause direct health care costs were $23,211 [38,599] per person-year; hospitalizations represented the largest cost driver (57.8%).

Conclusions: These results provide further understanding of the epidemiology of HD in Canada and highlight the burden of HD on the public health care system.

3

Bianca De Blasi*1, Hugo Dugdale1, Jack Weatheritt1, Marina Papoutsi1, Richard Joules1, Adam J. Schwarz2
1IXICO, Plc., London, UK
2Takeda Pharmaceuticals, Ltd., Cambridge, MA, USA

Background: Caudate volume is a well-established biomarker in Huntington’s disease (HD) used to assess disease progression and potential efficacy of interventions. Therefore, the estimation of accurate volume and volume-change measures in this region is highly important.

Objectives: To develop a fully automatic workflow for estimation of caudate volume and volume change using deep-learning approaches.

Methods: We retrospectively analyzed HD natural history datasets (HD=149; pre-HD=41; controls=50) with baseline and two-year follow-up T1W MR scans. Cross-sectional segmentations and caudate volumes were obtained with a 3D convolutional neural network (CNN). To measure longitudinal volume change, we trained a CNN to perform non-linear registration of serial MR image pairs. Volume-change measures were obtained from integration of the Jacobian determinants within baseline segmentations.

Results: We compared baseline caudate volume between groups estimated with: (1) fully automatic multi-ATLAS-based, (2) manually refined multi-ATLAS-based, and (3) CNN-based segmentations. All methods revealed significant differences between groups. Qualitatively, manually refined and CNN achieved comparable segmentations, with the latter enforcing a more consistent caudate-accumens boundary. Longitudinally, we compared caudate percentage volume change estimated with: (1) the Jacobian CNN method employing manually refined ATLAS and CNN baseline caudate segmentations and (2) a temporally coupled segmentation-based method initialized with manually refined ATLAS. The Jacobian method reported significantly reduced sample sizes (power:80%, α:0.05) for HD and pre-HD groups (with either manually refined ATLAS and CNN baseline caudate segmentations), when compared to the segmentation-based approach (HD Left/Right: CNN=90/116; ATLAS=168/218).

Conclusions: We present a fully automatic workflow for estimating caudate volume and volume change in a computationally efficient, scalable approach with advantages for clinical trials.

4

Psychological Interventions for People with Huntington’s Disease: A Call to Arms
Nicolò Zarotti*1, Maria Dale2, Fiona Eccles1, Jane Simpson1
1Division of Health Research, Faculty of Health and Medicine, Lancaster University, Lancaster, UK
2Adult Mental Health Psychology, Leicestershire Partnership NHS Trust, Leicester, UK

Background: Although Huntington’s disease (HD) can cause a wide range of psychological difficulties, no review has ever been carried out on the range of psychological interventions adopted with this population.

Objectives: To scope the literature on psychological interventions for psychological difficulties in people affected by HD.

Methods: A systematic scoping review was performed across MEDLINE, PsycINFO, CINAHL,
Methods: We examined swallowing, speech, language, and communication abilities in three patients with HD using clinical and instrumental evaluations and self-reported questionnaires, in combination with standardized outcome measures based on the ICF framework. The analysis was completed with a modified version of the Rehabilitation Problem Solving Form (RPS-Form). Finally, a set of ICF codes relevant to speech therapy was identified, and an ICF-based documentation tool was developed.

Results: The distribution of these codes across the ICF framework showed that the components of Body Functions, Activities and Participation, and Environmental Factors were almost equally represented. However, the analysis revealed that environmental factors, such as caregiver support, were both key barriers and facilitators to achieve successful outcomes in the late stages of HD.

Conclusions: These cases illustrate the usefulness of the ICF to conceptualize the complexity of late-stage rehabilitation in the home environment.

6

Knowledge Translation of a Clinical Practice Guideline for Physical Therapy Management of Persons with Huntington’s Disease

Anne D. Kloos¹, Deb A. Kegelmeyer¹, Ashwini Rao², Lori Quinn³, Nora Fritz*⁴

¹The Ohio State University, Columbus, OH, USA
²Columbia University, New York City, NY, USA
³Teachers College, University, New York City, NY, USA
⁴Wayne State University, Detroit, MI, USA

Background: Clinical guidelines provide a clear description of current best practices and may be especially useful in rare diseases. Our group recently published a clinical guideline for physical therapy (PT) management of persons with Huntington’s disease (HD).

Objectives: As a next step to implementation of these clinical guidelines into practice, we aimed to: (1) recommend clinical assessments based on available literature; (2) provide guideline-based decision trees to aid in decision-making; and (3) recommend strategies to overcome barriers and to facilitate implementation of the guidelines.

Methods: We conducted a literature search to identify PT assessments used in HD, as well as
Long-standing working relationships with the clinical sites have been built over time through the operational management of Enroll-HD, which enables well-informed site identification and feasibility based on extensive knowledge of sites’ capabilities, historic performance, and information about sites’ access to potential participants. This site intelligence is supported by both the Enroll-HD HD Clinical Trial Site Certification Scheme that assesses potential trial sites (within and outside Enroll-HD) against a set of standard minimum criteria for clinical trial participation and the Enroll-HD participant database that enables powerful in-silico screening using study-specific inclusion and exclusion criteria to identify potentially eligible participants who can be invited into interventional trials. In addition, the platform can provide support for participant referrals from neighboring Enroll-HD sites into the selected study sites.

8

Enroll-HD Clinical Trial Committee

Jenny Townhill1,2, Tim McLean1, Juliana Bronzova*, Cristina Sampaio3, and Swati Sathe3 (on behalf of the Enroll-HD Clinical Trial Committee)

1EHDN, Ulm, Germany
2Cardiff University, Cardiff, UK
3CHDI Management/CHDI Foundation, Princeton, NJ, 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 committee composed of HD expert clinicians and scientists, and has three main remits: (1) provision of advice on protocol design and clinical development topics, with access to experts from within the CHDI Clinical Department (imaging, biomarkers, clinical outcomes, and disease modeling) and/or independent HD experts from the CTC advisory panel; (2) review of final protocols by independent HD experts to allow access to Enroll-HD platform operational
support (e.g. in-silico feasibility, site identification, and recruitment support; see Enroll-HD Platform resource poster); and (3) oversight of the HD Clinical Trial Site Certification Program, open to Enroll-HD and non-Enroll-HD sites with the capabilities and expertise to be considered suitable for HD clinical trials. A Site Certification application group assesses sites’ suitability against a set of basic generic industry-agreed criteria.

9

The European Huntington’s Disease Network

Jenny Townhill1,2, Tim McLean*,1, Jamie Levey1,3, Anne Rosser2, Patrick Weydt4, Michael Orth5, and Christine Capper-Loup1,5 (all on behalf of EHDN Central Coordination)

1EHDN, Ulm, Germany
2Cardiff University, Cardiff, Wales, UK
3CHDI Foundation/CHDI Management, Princeton, NJ, USA
4University Hospital Bonn, Bonn, Germany
5Siloah, Gümligen, Switzerland

Background: The European Huntington’s Disease Network (EHDN), established in 2003, is a non-profit research network with the mission of advancing research, facilitating conduct of clinical trials, and improving clinical care in HD. EHDN forms a platform for clinicians, scientists, academics, patients, and family members to work together to achieve these goals.

The EHDN offers membership to those with an interest in/directly affected by HD; >200 European HD clinical and basic science centers and >3,400 individuals are members. EHDN hosts a bi-annual plenary meeting, one of the world’s largest conferences dedicated to Huntington’s disease. A fellowship exchange program has been established to facilitate training of young HD professionals from countries where HD care and facilities are developing.

The EHDN is governed by an Executive Committee, responsible for overseeing activities and establishing scientific strategy, with a Scientific Bioethical Advisory Committee responsible for reviewing research proposals. EHDN Central Coordination manages network operations, with regional Language Area Coordinators as the bridge between the EHDN and the clinical centers, liaising with the HD patient and research communities and monitoring Enroll-HD study and platform data.

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

EHDN Working Groups and Task Forces address key HD research topics, supported by the Think Tank, experts with in-depth knowledge of EHDN scientific activities. EHDN supports researchers with identifying grant and funding opportunities and by awarding seed funds. Clinical data and/or biosamples from the Registry study are available to researchers (see EHDN Scientific Support poster).

EHDN is supported by the CHDI Foundation and collaborates closely with CHDI and the Enroll-HD platform. www.ehdn.org

10

Client Attitudes Toward Confidential Genetic Testing in a Non-Medical Setting

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

HD Reach, Raleigh, NC, USA (all authors)

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. Typical medical and academic testing centers can be limited by an inability to offer confidential testing, a lack of psychiatric services, and cost.

Objectives: This study seeks to examine the personal experiences of at-risk individuals who have chosen to undergo genetic testing for HD in a non-medical genetic testing program.

Methods: Based on outcomes from a pilot program, a confidential and anonymous genetic testing program was created. The program incorporates bridge treatment during the decision-making and genetic-testing phases; facilitation of social supports for the client/testing partner; psychoeducation directed at coping skills; confidential/anonymous genetic testing using a standardized protocol; and tele-health technology to reach people regardless of location. All visits except for blood draws were completed virtually using a HIPAA-compliant online platform. Clients provided consent to being contacted for the
purpose of the program evaluation. The staff member who conducted evaluation interviews was not involved in the testing process.

**Results:** A total of 10 people who completed genetic testing for HD at a non-genetic testing program were included in this study. Six clients provided feedback. Four client interviews are pending. All clients who completed the evaluation felt the overall process met their needs. Clients described importance of confidentiality, decreased fear of unauthorized disclosure of data, and appointment flexibility. Obstacles reported included issues with internet connection, the need to go through psychological evaluations, and anxiety during check-ins.

**Conclusions:** Genetic testing in a non-medical setting is a viable option for people who are at risk for HD. Feedback received was overwhelmingly positive toward this option. Many clients who have completed this program have referred others who are at risk to this testing program.

---

**Lumbar Puncture Safety in People with Huntington’s Disease – A Multi-Study Cross-Sectional Survey**

Yara Hassan*, Filipe Brogueira Rodrigues, Paul Zeun, Lauren Byrne, Carlos Estevez Fraga, Rosanna Tortelli, Rachael Scahill, Edward Wild, and Sarah J. Tabrizi

*University College London, London, UK (all authors)*

**Background:** Lumbar puncture (LP) as a procedure has become increasingly relevant for people with Huntington’s disease (HD), both to administer intrathecal investigational medicinal products, such as antisense oligonucleotides, and to collect cerebrospinal fluid (CSF) to develop and validate biological markers to track disease stage and progression. Despite this increased utilization of LP procedures in HD, the literature is still unclear about its safety profile.

**Objectives:** We aimed to investigate the safety profile of LPs in people with HD.

**Methods:** We conducted a multi-study, cross-sectional survey—including eligible participants from the HDClarity (NCT02855476), HD-YAS (Scahill/Zeun et al, 2020), and NHS (NCT03664804; UCL cohort only) studies—collected between February 2016 to January 2020. Eligible participants were healthy controls and premanifest and manifest gene-expansion carriers. We investigated the odds of any adverse events, headaches, and back pain, independently. Intergroup comparisons and adjusted event odds were derived using hierarchical logistic regressions.

**Results:** A total of 684 LPs involving 500 study participants were included in this analysis (139 healthy controls, 179 premanifest HD, and 182 manifest HD). The detailed results of our analysis will be presented at the European Huntington’s Disease Network meeting.

**Conclusions:** The LP is safe in patients with HD.
(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. In both parts, Companion Participants will complete a Companion Information Form, a short questionnaire asking about the Companion Participant’s perceptions and experiences as a caregiver/companion to the mHDGEC Participant.

**Results:** A robust suite of training materials have been developed to train and certify HD-SIF and HDCSQ raters. This study is entering into the final phase of start-up with recruitment scheduled to run from 3Q2021 until 2023. Preliminary results from Part 1 will be available during 2022, and a full report will be available later that year.

**Conclusions:** 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. Including a more advanced patient population will empower them to participate and will promote their valued contribution to research.

**The European Huntington’s Disease Network (EHDN) Scientific Support**

Christine Capper-Loup and Michael Orth (on behalf of EHDN)

1 European Huntington’s Disease Network, Ulm, Germany
2 Neurozentrum Siloah, Gümligen, Switzerland
3 University Hospital of Old Age Psychiatry and Psychotherapy, Bern University, Bern, Switzerland

**Background:** The European Huntington’s Disease Network (EHDN) is an independent non-profit organization dedicated to advancing research, conducting clinical trials, and improving care for people affected by Huntington’s disease (HD). In order to advance research, EHDN has developed a number of strategies:

- 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 with submission deadlines on March 1 and November 1. The maximum sum available is EUR 50,000.
- 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 data set (RDS). The format is similar to the Enroll-HD periodic dataset (PDS), using the same recoded IDs, if researchers wanted to use both data sets. The procedure to obtain the RDS and renewable biosamples is straightforward with a review of the project by the Chairs of the EHDN Scientific and Bioethics Advisory Committee (SBAC) and Executive Committee (EC).
- The EHDN Think Tank complements and facilitates EHDN research initiatives such as the 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 or TFs.
- The EHDN Grant and collaborations manager can support HD researchers in identifying potential funding opportunities and collaborations.

EHDN is financially supported by the CHDI foundation.

**Medicinal Cannabis in Huntington’s Disease**

Peter K. Panegyres*

Neurodegenerative Disorders Research Pty. Ltd., West Perth, Western Australia, Australia

**Background:** Huntington’s disease (HD) is a complex neurodegenerative trinucleotide repeat disorder with limited treatment options. This study investigates the potential role of medicinal cannabis.

**Objectives:** Two sisters with stage III and IV HD requested treatment with medicinal cannabis, one with intractable chorea and the other with severe oromandibular dystonia and chorea resulting in such frequent tongue biting that every time she opened her mouth to talk or eat, she bit her tongue with severe pain and bleeding.

**Methods:** Sister 1 is 47 with manifest HD for 10 years with a CAG repeat length of 45. She had a computerized movement analysis, which confirmed
Abstracts

**Methods:** 155 subjects (33 HD, 28 PMgene+, 30 PMgene-, and 14 NC) underwent three ten-second static balance trials (eyes open [EO], eyes closed [EC]) using a force plate. Postural sway was quantified in anteroposterior (AP), mediolateral (ML), and total sway (TS) path lengths. Additionally, a continuous wavelet transform was performed to understand the frequency modulation of postural sway from 0-4 Hz.

**Results:** All subjects demonstrated greater postural sway in all directions with EC compared to EO (F3,99=6.725, p<.001 AP, F3,99=4.551, P<.005 ML, F3,99=6.131, P<.001 TS). HD subjects exhibited greater postural sway (40.96 cm ± 44.05 EO, 58.27 cm ± 59.38 EC) compared to PMgene+ (9.78 ± 3.24 EO, 16.08 ± 7.74 EC), PMgene- (9.40 ± 3.69 EO, 13.39 ± 7.00 EC), and NC (9.31 ± 3.11 EO, 13.10 ± 3.32 EC), especially with EC. HD subjects also exhibited significantly greater power in the COP spectrum from 0-4 Hz (F3,99=5.393 P< .002), especially with EC (F3,99=7.910 P< .001).

**Conclusions:** HD impairment in postural control in the absence of vision is indicative of a higher risk for falls. In addition, the quality of postural sway with sensory weighting seems to scale with progression to manifest HD.

17

**Novel Neuropsychological Tool in Pre-manifest Huntington’s Disease**

Luis A. Sierra Jr.*, Kaitlin Toal, Clementina J. Ullman, Samuel A. Frank, and Simon Laganiere

Beth Israel Deaconess Medical Center, Boston, MA, USA (all authors)

**Background:** Although the diagnosis of manifest HD is primarily based on motor symptoms, subtle cognitive decline is often one of the earliest symptoms and may go underrecognized or underappreciated. The LASSI-L has proven helpful in detecting early and subtle cognitive changes in Alzheimer’s disease by targeting deficits in proactive semantic interference (PSI), failure to recover from proactive semantic interference (frPSI), retroactive semantic interference (RSI), and semantic intrusion errors.

**Objectives:** We hypothesized that the Loewenstein Acevedo Scales of Semantic Interference and Learning (LASSI-L) would provide a sensitive measure of...

16

**Low-Frequency Oscillations in Postural Sway May Have Prognostic Value in Huntington’s Disease**

Harsimran S. Baweja*, Daniel J. Goble, Paul E. Gilbert, and Jody Corey-Bloom

1San Diego State University, San Diego, CA, USA
2Oakland University, Rochester, MI, USA
3University of California at San Diego, San Diego, CA, USA

**Background:** Predicting disease progression is important to the success of clinical trials involving pre-manifest (PM) HD subjects. Similarly, falls are a significant concern in HD; the ability to grade fall risk would be of substantial value.

**Objectives:** To determine if markers in postural sway have prognostic implications for fall risk and conversion to manifest HD.
Determining Plasma Neurofilament Light Cut-Off Points for Predicting Years to Manifest Huntington’s Disease Onset

Georgia M. Parkin*1,2, Jody Corey-Bloom3, Chase Snell3, Haileigh Smith3, and Elizabeth A. Thomas1,2

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

Background: The ability to predict when an individual is likely to transition to manifest Huntington’s disease (HD) is of substantial importance to the success of clinical trials involving premanifest HD (PM) subjects. We have previously determined that plasma neurofilament light (NfL) levels are significantly correlated with predicted years to manifest HD onset.

Objectives: In the current study, we aimed to extend our previous findings in a larger cohort, determine associations between plasma NfL and estimated years to manifest disease onset, and determine NfL cut-off points for predicting years to onset.

Methods: We administered the LASSI-L to 14 presymptomatic Huntington’s participants and 11 age- and education-matched healthy controls as part of a larger longitudinal research study aiming to detect novel biomarkers of disease progression. As a comparison, we also administered more established neuropsychological measures to both groups. Participants were also characterized along several other metrics, including CAG repeat length, demographics, education, and medical comorbidities.

Results: Three different indices on the LASSI-L showed group-wide differences in PSI (p = 0.016) and RSI (p = 0.030), and delay recall (p = 0.001). Adjusting for multiple comparisons (bonferroni correction), delayed recall remained significant. Traditional neuropsychological measures Trails B, Stroop Color naming/interference, SDMT, and Category Fluency (Animals) were not significantly different between groups. Adjusting for multiple comparisons (bonferroni correction), only the Stroop Word reading remained significant.

Conclusions: The LASSI-L appears to be a sensitive neuropsychological tool for detecting early cognitive changes in pre-symptomatic HD and may serve as a sensitive biomarker of cognitive change. The LASSI-L outperformed many traditional neuropsychological tasks routinely used in HD related research.

Demographics and Cognitive Baseline

<table>
<thead>
<tr>
<th></th>
<th>HD N=14</th>
<th>HC N=11</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (19-64 y)</td>
<td>36.00 (SD=10.6)</td>
<td>35.82 (SD=15.02)</td>
<td>0.97</td>
</tr>
<tr>
<td>Education (12-20 y)</td>
<td>15.14 (SD=2.80)</td>
<td>15.45 (SD=2.21)</td>
<td>0.97</td>
</tr>
<tr>
<td>Sex Female</td>
<td>71.4%</td>
<td>36.4%</td>
<td>0.08</td>
</tr>
<tr>
<td>MMSE Score</td>
<td>28.57 (SD=0.94)</td>
<td>29.45 (SD=0.69)</td>
<td>0.02</td>
</tr>
<tr>
<td>Category Fluency (Animals)</td>
<td>20.93 (SD=6.47)</td>
<td>23.08 (SD=6.22)</td>
<td>0.41</td>
</tr>
<tr>
<td>SDMT</td>
<td>48.93 (SD=10.86)</td>
<td>52.00 (SD=15.14)</td>
<td>0.56</td>
</tr>
<tr>
<td>STROOP Word Reading</td>
<td>81.86 (SD=12.29)</td>
<td>103.67 (SD=8.84)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>STROOP Color Naming</td>
<td>69.00 (SD=11.57)</td>
<td>82.00 (SD=10.03)</td>
<td>0.007</td>
</tr>
<tr>
<td>STROOP Interference</td>
<td>46.21 (SD=13.01)</td>
<td>55.00 (SD=13.23)</td>
<td>0.11</td>
</tr>
<tr>
<td>Trails A</td>
<td>34.50 (SD=13.48)</td>
<td>24.01 (SD=5.24)</td>
<td>0.02</td>
</tr>
<tr>
<td>Trails B</td>
<td>62.77 (SD=19.45)</td>
<td>61.58 (SD=20.00)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

longitudinal cognitive changes in pre-symptomatic HD over 18 months.
S12

Abstracts

Methods: This study included 148 (59 HD, 38 PM, and 51 normal control NC) participants recruited through the University of California San Diego’s Huntington’s Disease Society of America Center of Excellence. Plasma NfL levels were measured in duplicate using a Meso Scale Discovery R-PLEX Assay.

Results: Plasma NfL levels were significantly correlated with age and differed by cohort, both before and after correcting for age (all ps<0.001). A receiver operating characteristic curve analysis determined that a plasma NfL cut-point of <45.01 pg/ml could accurately distinguish participants with ≤10 vs. >10 predicted years until HD onset at 60% probability (AUC=0.86, p=0.0007; sensitivity=78.57%; specificity=100.0%), and those with ≤15 vs. >15 predicted years until HD onset at 70% probability (AUC=0.88, p=0.0002; sensitivity=80.77%; specificity=91.67%).

Conclusions: Incorporation of plasma NfL values into calculations for predicted years to HD onset may improve the accuracy of these estimates.

Demographics and Healthcare Resource Utilization (HRU) in U.S. Patients with Huntington’s Disease: Data from the Huntington’s Disease Burden of Illness (HDBOI) Study


1Harvard Medical School/BIDMC, Boston, MA, USA
2The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
3CHDI Foundation, Los Angeles, CA, USA
4Huntington’s Disease Youth Organization, Roanoke, VA, USA
5Huntington’s Disease Association, Liverpool, UK
6Huntington’s Disease Society of America, New York, NY, USA
7HCD Economics, Warrington, UK
8uniQure, Inc., Amsterdam, the Netherlands

Background: The prevalence of Huntington’s disease (HD) has increased over time; however, there is a lack of up-to-date evidence documenting the burden of HD by disease stage.

Objectives: This study aims to provide an overview of demographics and healthcare resource utilization in U.S. patients with HD who participated in the HDBOI study.

Methods: The HDBOI is a retrospective, cross-sectional dataset that captures sociodemographic, clinical variables and HRU of a cohort of HD patients reported by the treating physician. Statistical significance of differences by disease stage were assessed by ANOVA tests.

Results: The HDBOI U.S. sample has 492 HD patients, of which 43% were early stage (ES), 31% mid stage (MS), and 26% advanced stage (AS). Mean age was 46 years (SD± 13.7), and 61% were male. Most patients were insured privately (35%), followed by Medicare (27%) and Medicaid (26%); 4% did not have any insurance. Regarding HRU, the average number of visits per year to treating physician increased with disease severity (P<0.001): 3.2 (SD± 2.44) for ES; 4.2 (SD± 3.7) for MS; and 4.4 (SD± 3.2) for AS. A similar trend was observed for nurse visits (2.4 (SD± 2.88) for ES; 2.62 (SD± 3.6) for MS; and 3.19 (SD± 3.56) for AS). Hospitalizations were more frequent in AS patients (P<0.002) and 19.2% had at least one inpatient hospitalization vs. 6.6% and 10.4% in the ES and MS groups, respectively.

Conclusions: The HDBOI study provides novel data to quantify HRU use by disease stage, increasing the evidence base for the HD community.

CPEB Alteration and Aberrant Transcriptome-Polyadenylation Unveil a Treatable Vitamin B1 Deficiency in Huntington’s Disease

Sara Picó* and José J. Lucas

1Center for Molecular Biology “Severo Ochoa” (CBMOSO) CSIC/UAM, Madrid, Spain
2Networking Research Center on Neurodegenerative Diseases (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain

Background: Although promising gene-silencing therapies are being tested for Huntington’s disease (HD), no disease-modifying treatments are available. Thus, study of molecular mechanisms under-
neath Htt-mutation must continue to identify easily druggable targets. Cytoplasmic polyadenylation element binding proteins 1-4 (CPEB1-4) are RNA-binding proteins that repress or activate translation of CPE-containing transcripts by shortening or elongating their poly(A) tail. Alteration of CPEB-dependent transcriptome polyadenylation has been associated with diseases like cancer, autism, and epilepsy.

**Objectives:** The goals of this research are to analyze CPEBs and polyadenylation in HD and identify easily druggable targets among genes that are misexpressed due to altered CPEB-dependent polyadenylation, to assay them in HD mice.

**Methods:** (1) Western blot and immunostaining of CPEBs in brains of HD patients and mouse models. (2) Genome-wide poly(A)-tail analysis through poly(U) chromatography+gene chip. (3) Status of CPEB targets and related metabolites by western blot and HPLC. (4) Radiological, neuropathological, and behavioral analysis of HD mice receiving target-related treatment.

**Results:** There is a CPEB1/4 imbalance in HD striatum with concomitant altered transcriptome polyadenylation affecting many neurodegeneration-linked genes like PSEN1, MAPT, SNCA, LRRK2, PINK1, DJ1, SOD1, TARDBP, FUS, and HTT. Among top deadenylated genes was SLC19A3 (ThTr2 thiamine transporter), whose mutation causes biotin+thiamine responsive basal ganglia disease (BTBGD). Decreased ThTr2 in HD and HD mice led us to discover that HD is in part a BTBG-like thiamine deficiency. Remarkably, high dose biotin-thiamine treatment prevented the thiamine deficiency of HD mice and attenuated their radiological, neuropathological, and motor phenotypes.

**Conclusions:** This study unveils altered polyadenylation as a new molecular mechanism in neurodegeneration uncovering HD as a thiamine deficiency and, therefore, an easy to implement therapy.
Abstracts

21

Economic Burden of Huntington’s Disease Patients by Disease Stage in EU-5 and the USA: Preliminary Data from the Huntington’s Disease Burden of Illness Study (HDBOI)


1Harvard Medical School/BIDMC, Boston, MA, USA
2The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
3European Huntington’s Association, Moerbeke (Waas), Belgium
4Manchester Centre for Genomic Medicine, Manchester, UK
5BSMHFT, National Centre for Mental Health in Birmingham, UK
6CHDI Foundation, Los Angeles, CA, USA
7Huntington’s Disease Youth Organization, Roanoke, VA, USA
8Huntington’s Disease Association, Liverpool, UK
9Huntington’s Disease Society of America, New York, NY, USA
10Deutsche Huntington-Hilfe e.V, Duisburg, Germany
11HCD Economics, Warrington, UK
12University of Chester, Chester, UK

Background: The prevalence of Huntington’s Disease (HD) has increased over time, however there is a lack of up-to-date evidence documenting the economic burden of HD by disease stage.

Objectives: This study aims to provide an estimate of the annual direct medical (DMC), non-medical (DNMC), and indirect (IC) costs associated with HD of participants of the HDBOI study, by disease stage as assessed by the treating physician.

Methods: The HDBOI is a retrospective, cross-sectional study in which physicians reported information on patient characteristics, and health resource utilization (HRU) (used to compute DMC) of a cohort of HD patients in multiple centers across EU-5 and the U.S. Patients and caregivers reported information on NDMC and IC associated with HD through optional questionnaires. Data were collected between September 2020 and May 2021. Country-specific unit cost sources were used.

Results: HDBOI cost estimates were: €12,663 (N 2,094; SD €34,012) for DMC, €2,984 (N 359; SD €4,512) for DNMC, and €47,576 (N 436; SD €47,985) for IC. Costs are higher in patients who are at later stages of disease (e.g., DMC estimates were €9,220 (N 846, SD €31,855), €11,885 (N 701, SD €31,827), and €18,985 (N 547, SD €38,811) for early, mid, and advance stages, respectively). Similar trends were observed for DNMC and IC. Costs show large variations between patients and studied countries.

Conclusions: Cost estimates from the HDBOI study show that HD patients and caregivers bear a large economic burden that increases as disease progresses.

22

Development of the Huntington’s Disease Integrated Staging System (HD-ISS)


1University College London, London, UK
2F. Hoffmann-La Roche Ltd, Basel, Switzerland
3CHDI Management/CHDI Foundation, Los Angeles, CA, USA
4Novartis, Cambridge, MA, USA
5VectorY, Amsterdam, the Netherlands
6University of Ottawa, Ontario, Canada
7Wave Life Sciences, Cambridge, MA, USA
8Critical Path Institute, Tucson, AZ, USA
9Johns Hopkins University, Baltimore, MD, USA
10Vaccinex, Rochester, NY, USA
11University of Iowa, Iowa City, IA, USA
12Harvard Medical School/BIDMC, Boston, MA, USA

Background: While there is biological certainty that individuals with a pathogenic expansion in the huntingtin gene will develop the signs and symptoms of HD within a normal lifespan, this is not reflected in present terminology. Current staging methods do not address disease progression before an overt clinical phenotype, despite well-accepted biomarkers of neurodegeneration predating clinical diagnosis.

Objectives: To propose a new HD framework (the “HD-ISS”) that comprises an HD biological research definition and evidence-based staging centered on prognostic biological, clinical, and functional landmarks.

Methods: This framework is the result of a formal consensus process within the HD-RSC. Observational data were employed to calculate “cut-offs”
using the extreme values in models of the control population to define the HD-ISS Stages and to evaluate the framework.

**Results:** The HD-ISS characterizes individuals based on genetic expansion. The HD-ISS incorporates landmarks demonstrating robust prognostic value to classify individuals into each Stage and data-driven landmark thresholds to define Stage boundaries that are not CAG-dependent. Individual study visits, participant Stage progression, and longitudinal models of Stage progression align with the natural history of HD and with increased CAG predicting accelerated transitions.

**Conclusions:** The RSF has developed a biological definition of HD and an evidence-based staging system that encompasses the full course of the disease. The HD-ISS is primarily intended for research settings and provides a new structure to anchor and harmonize clinical study populations and facilitate assessment of interventions that prevent or delay the onset of HD symptoms. The immediate research use of the HD-ISS will allow for further validation.

**Exploring Outcomes of Long-Term Physical Activity and Exercise in People with Huntington’s Disease**

Lori Quinn*, Rebecca Playle, Cheney J.G Drew, Katie Taiyari, Rhys Williams-Thomas, Lisa Muratori, Ciaran P. Friel, Philippa Morgan-Jones, Hai-Jung Shih, Katy Hamana, Beth Ann Griffin, Mark Kelson, Robin Schubert, Anne Rosser, and Monica Busse

1Centre for Trials Research, Cardiff University, UK
2Teachers College, Columbia University, New York, USA
3George-Huntington-Institute and Institute for Clinical Radiology, University of Münster, Münster, Germany
4Stony Brook University, Stony Brook, NY, USA
5Center for Personalized Health, Northwell Health, New York, NY, USA
6School of Engineering, Cardiff University, UK
7School of Health Care Sciences, Cardiff University, UK
8RAND Corporation, Arlington, VA, USA
9Department of Mathematics, Exeter University, UK
10Schools of Medicine and Biosciences, Cardiff University, Cardiff, Wales, UK

**Background:** Physical therapist-led exercise is important in the management of people with Huntington’s disease (PwHD); however, long-term evaluation has yet to be undertaken.

**Objectives:** To explore outcomes of a 12-month longitudinal cohort study with a nested randomized controlled trial (RCT) of therapist-led exercise intervention compared to usual activity in people with early-mid stage HD.

**Methods:** Participants completed assessments at baseline and 12 months. The intervention consisted of 18 sessions over one year that included goal setting, use of wearable activity monitor, and disease-specific workbook.

**Results:** Fifty-nine individuals (25F; mean(SD) age 52(11)) were enrolled in the cohort and 53 in the RCT (31F; mean(SD) age 56(10)). For the RCT, mean(SD) adherence in the intervention group was 81(29)%. Three SAEs were reported but none were related to the intervention. Forty-two falls with eight recurrent fallers (>1 fall) were reported in the control group and 43 with six recurrent fallers in the intervention group. Prespecified intervention fidelity criteria were met. VO2max was 139.1 mL/kg/min [95%CI -44.0, 322.2] higher; six-minute walk test was 33.5 m [-5.2, 72.2] longer; and physical activity (IPAQ) was 1349.3 MET*min [-874.8, 3573.5] greater in the intervention group compared to control at one year after controlling for baseline differences.
Individuals in the cohort declined in almost all measures over the one-year period.

**Conclusions:** A one-year therapist-led exercise intervention was safe and feasible in PwHD. A model of care that incorporates early exercise engagement with sustained consultation with physical therapists is important in managing functional decline in PwHD.

### 24

**Huntingtin Maintains Mitochondrial Genome Integrity and Function**

Subrata Pradhan*1, Rui Gao1, Keegan Bush1, Nan Zhang2, Charlene Smith-Geater1, Anirban Chakraborty4, Eva L. Morozko1, Narattam Sikdar1, Jeffrey Snowden1, Tapas K. Hazra1, Albert R. La Spada1, Yogesh P. Wairkar1, Leslie M. Thompson3, and Partha S. Sarkar1

1Department of Neurology, University of Texas Medical Branch, Galveston, USA  
2Department of Neurology, Houston Medical Research Institutes, Houston, USA  
3Department of Psychiatry and Human Behavior, University of California, Irvine, USA  
4Department of Internal Medicine, University of Texas Medical Branch, Galveston, USA  
5Department of Neurology, Duke University School of Medicine, Durham, USA

**Background:** Huntington’s disease (HD) is a terminal neurodegenerative disease characterized by the presence of dysfunctional mitochondria in the affected neurons, and damaged mitochondria are thought to contribute to early neurotoxicity in HD.

**Objectives:** We set out to study whether normal HTT forms a transcription-coupled DNA repair (TCR) complex with mitochondrial transcription machinery to maintain mitochondrial genome integrity and function, and whether mutant HTT disrupts TCR activity and mitochondrial function in HD.

**Methods:** Chromatin immunoprecipitation (ChIP) was used to determine the possible interaction of HTT with mitochondrial DNA. Proximity ligation assay (PLA) and immunoprecipitation (IP), followed by mass spectrometric analysis, was performed to understand the possible interaction of HTT with mitochondrial transcription complex components. Long Amplicon quantitative PCR (LA-QPCR) analysis was performed to assess mitochondrial DNA (mtDNA) damage accumulation and the catalytic activity of the DNA repair enzyme, PNKP, in the control and HD subjects.

**Results:** We have found that HTT is present within mitochondria and forms a novel TCR with mitochondrial transcription complex components (e.g., POLRMT, POLGA, TFAM, TFB1M/2M, CSB, and PNKP). This complex stimulates mtDNA damage repair to maintain mitochondrial genome integrity and function. The presence of mutant HTT within the TCR complex impairs efficacy of DNA repair resulting in persistent accumulation of mtDNA damages in cell, mouse, and Drosophila models of HD. Persistent accumulation of damages in mtDNA impairs adequate expression of mitochondrial genes compromising mitochondrial function. Restoring activity of the TCR complex in a Drosophila model of HD dramatically improves mtDNA integrity and motor coordination defects.

**Conclusions:** HTT plays a crucial role in maintaining mitochondrial genome integrity and function.

### 25

**Listener Detection of Objectively Validated Acoustic Features of Speech in Huntington’s Disease**

Jess Chan1, Julie Stout2, Chris Shirbin2, and Adam P. Vogel*1,3

1The University of Melbourne, Melbourne, Australia  
2Monash University, Victoria, Australia  
3Redenlab Inc., Melbourne, Australia

**Background:** Subtle progressive changes in speech motor function and cognition begin prior to diagnosis of Huntington’s disease (HD).

**Objectives:** To determine the nature and magnitude of listener-rated differences in speech and acoustic voice features in premanifest and early-stage HD (i.e., PreHD and EarlyHD) compared to neurologically healthy controls, and to relate these features to a commonly used cognitive measure of processing speed.

**Methods:** We administered a speech battery to 60 adults (16 people with PreHD, 14 with EarlyHD, and 30 neurologically healthy controls), along with a cognitive test of processing speed/visual attention, the Symbol Digit Modalities Test (SDMT). Voice recordings were rated by expert listeners and analyzed for acoustic and perceptual speech features.

**Results:** Listeners perceived subtle differences in the speech of PreHD compared to controls, including abnormal pitch level and speech rate, reduced
loudness and loudness inflection, dysphonic voice quality, hypernasality, imprecise articulation, and reduced naturalness of speech. In terms of acoustics, listeners detected significant slowing in the rate of speech in PreHD compared to healthy speakers on a reading task, which correlated with the perceptual judgement of abnormal speech rate and a lower cognitive performance. In early-stage HD, continuous speech was characterized by longer pauses, a higher proportion of silence, and slower rate compared to both PreHD and control groups.

Conclusions: Differences in speech and voice acoustic features are detectable in premanifest HD compared to healthy speakers by listeners and align with some acoustically derived objective speech measures. Slower speech rate in PreHD suggests altered oral motor control and/or subtle cognitive deficits that begin prior to diagnosis. Speakers with EarlyHD exhibited more silences compared to the PreHD and control groups, raising the likelihood of a link between speech and cognition that is not yet well characterized in HD.

26

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

Rebecca Mason*,1, Marina Papoutsi1,2, Beth Ann Griffin1,2, Catherine Martin1, Bonnie Hennig-Trestman1,4, Oliver Quarrell1, and Lauren Byrne1,6

1Huntington’s Disease Youth Organization (HDYO), Roanoke, VA, USA
2IXICO, London, UK
3RAND Corporation, Arlington, VA, USA
4Virginia Tech Carilion, Roanoke, VA, USA
5Sheffield Children’s NHS Foundation Trust, Sheffield, UK
6University College London, London, UK

Background: Huntington’s disease (HD) is a rare inherited neurodegenerative disorder with a typical onset between the ages of 30-50. Juvenile onset Huntington’s disease (JoHD), defined by 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 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 Q3 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.

27

Impact of Huntington’s Disease in Health-Related Quality of Life, Functioning, and Well Being from the Patient’s Perspective: The PERSPECTIVES-HD Study

Jesus Pérez Perez*,1, Jose Luis Lopez Sendón2, Saúl Martinez-Horta1, Jorge Mauriño3, Cristina García Bernaldez3, and Sofía García López3

1Hospital de la Santa Creu y Sant Pau, Barcelona, Spain
2Hospital Universitario Ramón y Cajal, Madrid, Spain
3Roche Farma S.A., Madrid, Spain

Background: Huntington’s disease (HD) causes a clinically evident high impact on the patient’s life from the premanifest stage, but there is lack of information about the perception of health-related quality of life from the patients’ perspective.

Objectives: The PERSPECTIVES-HD study aims to assess health-related quality of life and well-being using a standardized battery of patient-reported instruments. Frequency and temporal sequence of the motor, behavioral, and cognitive symptoms of the disease and their impact will also be studied.

Methods: A non-interventional, cross-sectional study will be conducted in 17 hospitals in Spain. Patients aged ≥18 years, with genetically confirmed HD diagnosis and an Independence Scale score ≥70, will be invited to participate. Main outcome measures
will be the Huntington’s Disease Health-Related Quality of Life and the Satisfaction with Life scales. Additional outcomes will be collected, including motor function (UHDRS-TMS), independence (HD Activities of Daily Living Scale), cognition (Stroop Color and Word-reading Test, Symbol Digit Modalities Test), mood (Beck Depression Inventory-Fast Screen), behavioral disturbances (Problem Behaviours Assessment for HD—short Version), perception of stigma (Stigma Scale for Chronic Illness), subjective disease perception (Brief Illness Perceptions Questionnaire), coping strategies (General Self-Efficacy Scale), and perception of hopelessness (Beck Hopelessness Inventory). Use of resources (direct and indirect) will also be collected.

Results: Patient recruitment began in May 2021 with a planned sample of 102 patients. The study is currently ongoing.

Conclusions: The study results aim to provide the patients’ perceptions about their own illness that could build a better understanding of the impact of living with HD.

28

SIGNAL Phase 2 Study Suggests that Pepinemab, Anti-SEMA4D Antibody, Provides Cognitive Benefit in Early Manifest Huntington’s Disease

E. Evans*1, M. Zauderer1, T. Fisher1, V. Mishra1, A. Reader1, C. Mallow1, D. Oakes2, J. Wittes3, E. Siemers4, E. Smith1, J. Leonard1, and A. Feigin5 for the Huntington Study Group

1Vaccinex, Inc., Rochester, NY, USA
2University of Rochester, Rochester, NY, USA
3Statistics Collaborative, Washington, D.C., USA
4Siemers Integration LLC, Zionsville, IN, USA
5New York University, Grossman School of Medicine, New York City, NY, USA

Background: Pepinemab (VX15/2503) antibody blocks the binding of semaphorin 4D (SEMA4D) to its plexin receptors. SEMA4D is upregulated in diseased neurons and triggers reactive astrogliosis. SIGNAL is a completed Phase 2 placebo-controlled study of pepinemab in HD.

Objectives: To determine safety and efficacy of pepinemab as a treatment for people with early manifest or prodromal HD.

Methods: The SIGNAL study included 179 subjects with early manifest (EM) disease (CAG repeat length ≥36, DCL 4, and TFC 11-13) and 89 subjects diagnosed as late prodromal (CAG ≥36 and DCL 2 or 3). Subjects were randomized 1:1 for monthly treatment with either 20 mg/kg pepinemab or placebo for at least 18 months.

Results: Pepinemab was well tolerated and detected in cerebrospinal fluid at the dose level targeted for biological efficacy. Co-primary efficacy measures consisted of a two-item HD cognitive assessment family, including One Touch Stockings of Cambridge (OTS) and Paced Tapping (PTAP) components of the HD-Cognitive Assessment Battery (HD-CAB), and Clinical Global Impression of Change (CGIC), a global measure of clinical meaningfulness. Although the primary endpoints did not achieve statistical significance, positive trends in the direction of pepinemab benefit were observed and were supported by additional analysis of secondary and exploratory endpoints. (1) A trend toward treatment benefit was observed in 6/6 components of the HD-CAB resulting in a highly significant HD-CAB composite score (p=0.007). In a posthoc subgroup analysis of subjects stratified by Montreal Cognitive Assessment scores (MoCA), the benefit of treatment was particularly striking in EM subjects with mild cognitive impairment at baseline (MoCA <26). (2) Posthoc analysis also indicated significant treatment benefit (p=0.0291) in the Apathy severity subscore of Problem Behaviors Assessment (PBA-s). Apathy has been previously reported to correlate with cognition in HD as well as in Alzheimer’s and Parkinson’s disease. (3) Prespecified exploratory FDG-PET imaging demonstrated that pepinemab treatment slowed or reversed decline in metabolic activity in 26/26 brain regions examined, with 15/26 regions showing a significant positive treatment effect (p≤0.05).

Conclusions: Although the SIGNAL phase 2 study did not meet its co-primary endpoints, significant treatment-related changes in HD-CAB Composite score, Apathy severity, and FDG-PET imaging support a potential cognitive benefit. Multiple clinical studies in AD have shown that decline in FDG-PET correlates with cognitive decline, and FDG-PET is accepted as a biomarker of clinical progression in AD. In contrast, other prespecified endpoints unrelated to cognition, including TMS and other UHDRS scales, did not indicate treatment benefit. This may be related to the relatively early stage of disease, TFC 11-13, of subjects enrolled in this study. These results will inform the design of a future phase 3 study in HD.
Disparities in Palliative Care Utilization Among Hospitalized People with Huntington’s Disease: A National Cross-Sectional Study

Leonard L. Sokol*1,2, Danny Bega1, Chen Yeh1, Benzi M. Kluger4, and Hillary D. Lum5

1The Ken and Ruth Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
2McGaw Bioethics Scholars Program, Center for Bioethics and Humanities, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
3Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
4Departments of Neurology and Medicine, University of Rochester Medical Center, Rochester, NY, USA
5Division of Geriatric Medicine, University of Colorado School of Medicine, Aurora, CO, USA

Background: Whereas nearly two-thirds of people with Alzheimer’s dementia die in skilled nursing facilities, the leading place of death among people with Huntington’s disease (HD) is within the hospital. In the U.S., approximately 5% of people with HD report utilizing palliative care (PC), despite studies indicating its significance in HD and its influence on improving quality of life/goal-concordant care in other illnesses. Given the high rates of in-hospital deaths, an understanding of the factors associated with PC utilization and its influence on goal-concordant care within the hospital setting is essential.

Objectives: Among hospitalized people with HD, our aims were first to determine the clinical, demographic, and social factors associated with PC utilization and, second, to evaluate the relationship between discharge disposition and PC utilization.

Methods: Using two multivariate logistic regression models, we analyzed 8,521 HD hospitalizations from 2007-2014 from the National/Nationwide Inpatient Sample, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality.

Results: Adjusting for covariates, factors associated with PC included primary insurer (private vs. Medicare; odds ratio: [OR 95% CI] 1.06-3.27), median household income (top quartile vs. bottom; OR: 1.06-2.95), DNR order (OR: 6.67-11.47), aspiration pneumonia (OR: 1.07-1.92), and respiratory failure (OR: 1.03-2.08). Depression was negatively associated with PC utilization. Those who received PC had a higher OR of discharge to a home with services (OR: 1.57-3.23) and a lower OR (OR: 0.32-0.58) of discharge to a nursing facility.

Conclusions: Adaptation of HD-PC models will need to surmount inequities to provide just access to PC services.

Symptom Burden of People with High vs. Low Meaning and Purpose in Huntington’s Disease

Leonard L. Sokol*1,2, Jonathan P. Troost3, Jane S. Paulsen4, Benzi M. Kluger5, Danny Bega1, Allison J. Applebaum6, Crystal L. Park7, Samuel Frank8, Jody Corey-Bloom9, Colin A. Depp10, David Cella11, and Noelle E. Carlozzi12

1The Ken and Ruth Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
2McGaw Bioethics Scholars Program, Center for Bioethics and Humanities, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
3Michigan Institute for Clinical and Health Research, University of Michigan, Ann Arbor, MI, USA
4Department of Neurology, University of Wisconsin-Madison, Madison, WI, USA
5Departments of Neurology and Medicine, University of Rochester Medical Center, Rochester, NY, USA
6Department of Psychiatry & Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, NY, USA
7Department of Psychological Sciences, University of Connecticut, Mansfield, CT, USA
8Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
9Department of Neurosciences, University of California San Diego, San Diego, CA, USA
10Department of Psychiatry, University of California, San Diego, San Diego, CA, USA
11Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
12Department of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor, MI, USA

Background: People with Huntington’s disease (HD) who have high meaning and purpose (M&P) experience elevated joy, independent of the symptom severity. However, how the health-related quality of life (HRQoL) and clinician ratings of symptoms and behavior (PBA) are associated with
levels of M&P within HD is unknown. As neuropa-liative specialists seek to enhance M&P, identifying
the factors explaining levels of M&P is essential to
optimize interventions.
**Objectives:** Adjusting for clinical/demographic co-
variates among people with HD and varying levels
of M&P, our aims were to: (1) compare the physical,
social, emotional, and cognitive HRQoL PROs; (2)
compare 11 HD-validated PBA evaluations; and (3)
determine what HRQoL PROs account for the vari-
ance of M&P.

**Methods:** 322 people with HD completed PROs/
PBAs at baseline, 12, and 24 months through
HDQLIFE. Groups were divided into low/medium/
high M&P (normal distribution and low/medium with
one standard deviation above/below). ANCOVA
models were used for each PRO/PBA item for Aims
1/2. Aim 3 used a multivariate time-varying nested
model.

**Results:** Compared to people with low M&P, peo-
ple with high M&P performed better on the Symbol
Digit Modalities test, had better emotional/social
HRQoL, and PBAs (i.e., less aggression, anxiety,
apathy, depression, irritability, suicidal behavior,
and hallucinations), and higher global HRQoL. De-
pression, advance care planning (ACP), positive af-
fect, and social satisfaction accounted for 29% of
M&P’s variance.

**Conclusions:** A distinct M&P phenotype may exist
within HD such that these people may experience a
better cognitive, emotional/social HRQoL. M&P in-
terventions should incorporate ACP and find alter-
native pathways to achieving social satisfaction.

31

**Concern with Death and Dying in
Huntington’s Disease: Associated
Domains and Longitudinal Outcomes**

Leonard L. Sokol*1,2, Jonathan P. Troost3, Danny Bega4,
Jane S. Paulsen4, Benzi M. Kluger5, Allison J.
Applebaum6, Samuel Frank7, Jody Corey-Bloom8, Colin
A. Depp9, David Cella1,10, and Noelle E. Carlozzi11

1The Ken and Ruth Davee Department of Neurology,
Northwestern University Feinberg School of Medicine,
Chicago, IL, USA
2McGaw Bioethics Scholars Program, Center for
Bioethics and Humanities, Northwestern University
Feinberg School of Medicine, Chicago, IL, USA
3Michigan Institute for Clinical and Health Research,
University of Michigan, Ann Arbor MI, USA
4Department of Neurology, University of Wisconsin-
Madison, Madison, WI, USA
5Departments of Neurology and Medicine, University of
Rochester Medical Center, Rochester, NY, USA
6Department of Psychiatry & Behavioral Sciences,
Memorial Sloan Kettering Cancer Center, New York, NY,
USA
7Department of Neurology, Beth Israel Deaconess
Medical Center, Harvard Medical School, Boston, MA,
USA
8Department of Neurosciences, University of California
San Diego, San Diego, CA, USA
9Department of Psychiatry, University of California, San
Diego, San Diego, CA, USA
10Department of Medical Social Sciences, Northwestern
University Feinberg School of Medicine, Chicago, IL,
USA
11Department of Physical Medicine and Rehabilitation,
University of Michigan, Ann Arbor, MI, USA

**Background:** Death anxiety appears as a persistent
trait across the lifespan among people with Hunting-
ton’s disease (HD) and was recently captured as a
patient-reported outcome (PRO): “HDQLIFE Con-
cern with Death and Dying (CwDD).” While pallia-
tive interventions in oncology have ameliorated death
anxiety, there are none within HD. Before adapting
neuropalliative interventions to HD, an account of
what PROs explain the variance of CwDD and how
CwDD predicts 12- and 24-month health-related
quality of life (HRQoL) outcomes would be helpful.

**Objectives:** Aim 1: Identify HRQoL domains asso-
ciated with the CwDD. Aim 2: Determine the 12-
and 24-month HRQoL PROs associated with
baseline CwDD.

**Methods:** 322 people from the multicenter
HDQLIFE study completed PROs at baseline, 12,
and 24 months. Aim 1 used a nested multivariate
model. Aim 2 used a linear mixed model while ac-
counting for baseline HRQoL outcomes and other
clinical/demographic factors.

**Results:** Twenty-eight percent of the variance in the
CwDD could be explained by stigma, PAW,
depression, anxiety, and swallowing difficulties.
Stigma had the most pronounced effect on the
variance of CwDD and how CwDD predicts 12-
and 24-month increases in anger, depression, and
impulsivity and decreases in meaning and purpose
(M&P), and positive affect and well-being (PAW)
(p < 0.05). In longitudinal mediation analysis, CwDD
had the most significant magnitude of predictiv-effect for depression.
Conclusions: CwDD and M&P may coalesce to influence depression. CwDD may predictably attenuate M&P, whereas M&P had no predictive effect on CwDD. Addressing CwDD should be incorporated within neuropalliative interventions for HD.

Meaning and Purpose in Huntington’s Disease: A Longitudinal Study of its Impact on Health-Related Quality of Life

Leonard L. Sokol*1,2, Jonathan P. Troost1, Benzi M. Kluger1, Allison J. Applebaum7, Jane S. Paulsen8, Danny Bega1, Samuel Frank2, Joshua M. Hauser6, Nicholas R. Boileau7, Colin A. Depp10, David Cella1,11, and Noelle E. Carlozzi9

1The Ken and Ruth Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
2McGaw Bioethics Scholars Program, Center for Bioethics and Humanities, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
3Michigan Institute for Clinical and Health Research, University of Michigan, Ann Arbor MI, USA
4Departments of Neurology and Medicine, University of Rochester Medical Center, Rochester, NY, USA
5Department of Psychiatry & Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, NY, USA
6Department of Medicine, Feinberg School of Medicine and Palliative Care Service, Jesse Brown VA Medical Center, Chicago, Illinois, USA
7Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
8Department of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor, MI, USA
9Department of Psychiatry, University of California, San Diego, San Diego, CA, USA

Background: In advanced cancer or AIDs, meaning and purpose (M&P) is protective against depression and suicidality, and increases the health-related quality of life (HRQoL), regardless of the magnitude of symptoms (e.g., pain or fatigue). Within Huntington’s disease (HD), recent findings have suggested that the strongest association with a sense of M&P was positive affect and well-being (PAW), which captures the experience of joy, happiness, and contentment with life. However, data were lacking regarding whether that relationship may be lessened by the magnitude of other HD-validated HRQoL patient-reported outcomes (PROs) and how M&P predicts longitudinal changes among various HRQoL PROs.

Objectives: Aim 1: Determine whether HD-validated physical, emotional, social, or cognitive HRQoL influence the relationship between M&P and PAW. Aim 2: Evaluate the 12- and 24-month changes in HRQoL associated with baseline M&P.

Methods: 322 people with HD received PRO and clinician assessments at baseline, 12-, and 24-months. A multivariate mixed-effects model was employed to assess the strength between M&P and PAW, utilizing HRQoL PROs as moderators and assessing for interactions between M&P and a PRO. A linear mixed-effects model was used to assess longitudinal changes.

Results: Higher M&P was associated with Higher PAW, independent of disease stage and the magnitude of HRQoL PROs (p < 0.001). Baseline M&P predicted decreases in depression, anxiety, anger, impulsivity, cognitive decline, and increases in PAW at 12 and 24 months (p < 0.05).

Conclusions: Our findings justify adapting meaning-centered palliative interventions to HD.

Advance Care Planning in Huntington’s Disease: Results from a Multicenter Study

Leonard L. Sokol*1,2, Jonathan P. Troost1, Danny Bega1, Jane S. Paulsen8, Benzi M. Kluger1, Hillary D. Lum9, Samuel Frank2, Colin A. Depp10, David Cella1,11, Noelle E. Carlozzi10

1The Ken and Ruth Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
2McGaw Bioethics Scholars Program, Center for Bioethics and Humanities, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
3Michigan Institute for Clinical and Health Research, University of Michigan, Ann Arbor MI, USA
4Department of Neurology, University of Wisconsin-Madison, Madison, WI, USA
5Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
6Department of Psychiatry & Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, NY, USA
7Department of Family Medicine, University of Rochester Medical Center, Rochester, NY, USA
8Department of Psychiatry, Feinberg School of Medicine and Palliative Care Service, Jesse Brown VA Medical Center, Chicago, Illinois, USA
9Department of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor, MI, USA
10Department of Medicine, Feinberg School of Medicine, Chicago, IL, USA

Background: In advanced cancer or AIDs, meaning and purpose (M&P) is protective against depression and suicidality, and increases the health-related quality of life (HRQoL), regardless of the magnitude of symptoms (e.g., pain or fatigue). Within Huntington’s disease (HD), recent findings have suggested that the strongest association with a sense of M&P was positive affect and well-being (PAW), which captures the experience of joy, happiness, and contentment with life. However, data were lacking regarding whether that relationship may be lessened by the magnitude of other HD-validated HRQoL patient-reported outcomes (PROs) and how M&P predicts longitudinal changes among various HRQoL PROs.

Objectives: Aim 1: Determine whether HD-validated physical, emotional, social, or cognitive HRQoL influence the relationship between M&P and PAW. Aim 2: Evaluate the 12- and 24-month changes in HRQoL associated with baseline M&P.

Methods: 322 people with HD received PRO and clinician assessments at baseline, 12-, and 24-months. A multivariate mixed-effects model was employed to assess the strength between M&P and PAW, utilizing HRQoL PROs as moderators and assessing for interactions between M&P and a PRO. A linear mixed-effects model was used to assess longitudinal changes.

Results: Higher M&P was associated with Higher PAW, independent of disease stage and the magnitude of HRQoL PROs (p < 0.001). Baseline M&P predicted decreases in depression, anxiety, anger, impulsivity, cognitive decline, and increases in PAW at 12 and 24 months (p < 0.05).

Conclusions: Our findings justify adapting meaning-centered palliative interventions to HD.
**Background:** Advance care planning (ACP) is a re-occurring process that entails a person with a serious illness conveying thoughts and decisions about current/future care to trusted persons and healthcare professionals. Within HD, ACP arose as a critical concern among key HD stakeholders and was conceptualized as the HDQLIFE End of Life Planning (EOLP) questionnaire. Despite these developments, people with HD do not complete documentation of ACP at any higher rate than the age-matched population. Moreover, some clinicians may fear that broaching EOLP could precipitate emotional harm, given HD’s elevated rates of suicidal ideation (SI).

**Objectives:** (1) To identify how much variance in EOLP is explained by different health-related quality of life (HRQoL) domains. (2) To determine if baseline EOLP predicts changes in HRQoL patient-reported outcomes (PROs) at 12 and 24 months.

**Methods:** PROs were collected at baseline, 12, and 24 months from 322 people with HD through the multi-center HDQLIFE study.

**Results:** PROs explained <5% of the variance in the EOLP. Baseline EOLP and its subdomains did not predict significant emotional/social PROs changes after adjusting for multiple comparisons.

**Conclusions:** Our data are consistent with past studies that suggest that ACP will not engender negative psychological states. Stakeholders do not need to fear that it will serve as a predictive marker for future emotional harm, including SI, and could thus normalize ACP during clinical encounters. A structured ACP process integrated within an existential M&P intervention may be warranted for this population.
The Exploration of Establishing a Wechat-Based Virtual Huntington’s Disease Cohort

Li-Shan Lin* and Zhong Pei

Department of Neurology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China (all authors)

Background: Inaccessibility to Huntington’s disease (HD) specialists, due to economic and time burdens, prevents patients from clinical trials, which is magnified by the COVID-19 pandemic. Wechat, a multi-functional app, which can exchange all formats of messages and has video calls, is widely used in China. It prompts us to explore a new clinical research model for HD.

Objectives: To establish a Wechat-based virtual HD cohort and verify its feasibility.

Methods: Based on the Wechat platform, the patients need to finish the self-reported questionnaires and upload the videos, as referred, which will be evaluated by researchers or AI. Then, a virtual visit and clinic visit will be conducted. The virtual follow-up visit will be arranged depending on the need.

Results: From December 2020 to July 2021, we enrolled 39 patients to participate in our study. All participants finished at least one visit, with more than half of the participants (64.10%, 25/39) finishing both the clinic and virtual visits; eleven finishing the virtual visit; and the other three finishing the clinic visit. Sixteen of them had at least one follow-up virtual visit.

Conclusions: It seems feasible to establish a virtual HD cohort based on Wechat. The cohort can be used to observe HD patients’ natural histories and assist in traditional clinical trials.

Pridopidine Rescues Pre- and Postsynaptic events in Huntington’s Disease Corticostriatal Network-on-a-Chip

Chiara Scaramuzzino¹, Sophie Lenoir¹, Romane Lahaye¹, Wilhelm Christaller¹, Hélène Vitet¹, Aurélie Genoux¹, Michal Geva², Michael Hayden²,³, and Frédéric Saudou¹

¹Grenoble Institut Neuroscience, Univ. Grenoble Alpes, Inserm, Grenoble, France
²Prilenia Therapeutics, Israel
³The Centre for Molecular Medicine and Therapeutics, BC Children’s Hospital Research Institute, University of British Columbia, Vancouver, British Columbia, Canada

Background: Pridopidine is a highly selective and potent Sigma-1 receptor agonist (S1R) in clinical development for HD and ALS. The S1R is located at the endoplasmic reticulum (ER)-mitochondria interface, where it regulates key cellular pathways impaired in neurodegenerative diseases. Alterations in BDNF levels and transport are hallmarks of neurodegenerative diseases and are directly affected by the mutant huntingtin protein in HD. Pridopidine demonstrates S1R-mediated neuroprotective effects in several preclinical models of HD, including enhancing BDNF signaling and mitochondrial function, restoring synaptic plasticity, and promoting pro-survival pathways.

Objectives: Assess the effects of pridopidine on presynaptic dynamics, synaptic transmission, postsynaptic trafficking, and signaling, as well as on global network dynamics.

Methods: Corticostriatal networks were reconstituted in microfluidic chambers from primary HD mouse model HTTCAG140/+ cells. The effects of pridopidine were evaluated on presynaptic BDNF transport, synaptic transmission, and post-synaptic signaling using advanced imaging techniques.

Results: BDNF trafficking is significantly diminished in HD neurons, with decreased velocity, number of motile vesicles, and global flow. Pridopidine rescues the number and velocity of secreted BDNF vesicles, restoring BDNF presynaptic flow. Pridopidine rescues impaired glutamate release from HD neurons, improving cortical synaptic function. Finally, pridopidine increases phospho-ERK in the post-synaptic striatal compartment, which is downstream to BDNF signaling and propagates survival signals. Importantly, pridopidine’s effect is completely abolished by the S1R antagonist NE-100, indicating that it acts exclusively via the S1R.

Conclusions: Pridopidine restores pre- and postsynaptic functions in an HD cellular model. The neuroprotective effects of pridopidine are exclusively mediated by S1R activation.
New Findings on the Mechanisms Driving Pridopidine’s Biphasic Dose Response

Michal Geva¹, Shao-Ming Wang², Hsiang-en Wu³, Noga Gershoni-Emek¹, Jing Jin¹, Christopher A. Ross³, Tsung-Ping Su², and Michael R. Hayden¹,⁴

¹Prilenia Therapeutics, Israel
²Cellular Pathobiology Section, Integrative Neuroscience Research Branch, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, USA
³Division of Neurobiology, Departments of Psychiatry, Neurology, and Neuroscience, Johns Hopkins University, Baltimore, MD, USA
⁴CMMT, University of British Columbia, Vancouver, Canada

Background: Pridopidine is a selective and potent Sigma-1 receptor (S1R) agonist in clinical development for Huntington’s disease (HD) and ALS. The S1R exerts neuroprotective functions and regulates nucleocytoplasmic transport (NCT), which is impaired in HD, by interacting with the nucleoporin protein POM121. S1R agonists are characterized by a biphasic dose response, with highest efficacy at an optimal dose and diminished efficacy lower and higher doses. Pridopidine demonstrates a biphasic dose response in vitro (i.e., in BDNF release, homeostatic plasticity, mitochondrial membrane potential, and cell viability assays). In PRIDE-HD, optimal clinical efficacy for maintaining total functional capacity was observed at 45 mg bid, with less effect at higher doses (67.5, 90, and 112.5 mg bid).

Objectives: To study pridopidine’s biphasic dose response in a cell toxicity assay and its effect on NCT.

Methods: We used primary HD neurons, S1R-BiP dissociation, and S1R oligomerization assays (NSC-34 cells). When bound to the ER protein BiP or in an oligomer, the S1R is inactive. At optimal doses, agonists facilitate S1R-BiP dissociation and promote S1R monomers.

Results: Pridopidine is protective against mHTT toxicity in a biphasic manner (optimal dose 1μM). At higher doses (10 and 100μM) pridopidine’s neuroprotective effect decreases. Pridopidine causes S1R-BiP dissociation and reduces S1R oligomerization in a biphasic manner (optimal dose 1μM), suggesting a potential mechanism driving the biphasic response of pridopidine. Pridopidine potentiates NCT, facilitating S1R-POM121 stabilization, in a biphasic manner.

Conclusions: Pridopidine acts as a S1R agonist displaying the typical biphasic neuroprotective dose response and enhancing NCT.
in the TRACK-HD study (ΔNfL +0.06 log2 pg/ml). Pridopidine 45 mg bid shows stabilization of NfL levels at 52 weeks (ΔNfL -0.06 log2 pg/ml, n=31). In placebo, the increase in NfL correlates with a decrease (worsening) in TFC (p=0.02). In the pridopidine 45 mg bid group, stabilization of plasma NfL is associated with maintenance of TFC.

Conclusions: Pridopidine 45 mg bid stabilizes plasma NfL levels in association with maintenance of TFC at 52 weeks in early HD.

Pre-Symptomatic Huntington’s Disease Support (REACT-HD) Group: A Survey of People’s Experience of an Online Support Group During the COVID Pandemic

Sandra Bartolomeu Pires*, Fiona Chaabane†, Emily Pond†, Jessica Harvey†, and Christopher Kipps†,‡

1University Hospital Southampton, Southampton, UK
2NIHR Applied Research Collaboration Wessex, Southampton, UK
3University of Southampton, School of Health Sciences, Southampton, UK
4Dementia, UK
5University of Southampton, Faculty of Medicine, Southampton, UK

Background: People in the pre-symptomatic Huntington’s disease (HD) stage have specific needs that are not being met by current care and support systems.

Objectives: To explore the support and educational needs of people in pre-symptomatic HD stage and assess their experience of attending a regular virtual group.

Methods: Sessions were delivered by clinicians via Zoom, quarterly, from January to July 2021. Attendees’ experiences were assessed through anonymous surveys.

Results: A pilot survey involving four patients and four carers identified four themes: (1) What to expect from HD in the future; (2) tips to keep healthy; (3) how HD is impacting your life and the life of others; and (4) research update (This theme was requested at every session). Sessions were organized around these themes. Seventeen people were invited. Attendance ranged from 6-11. They described the positive impacts of being able to meet and empathize with others in a similar situation and of the regular research updates, and the benefit of tailored education and discussions. Surveys showed all participants were “Very satisfied” with both session length (1 hour) and the session delivery and content.

Conclusions: People living with pre-symptomatic HD have particular support and education needs that are not addressed by current services. User-driven group sessions tailored to the individuals’ needs showed positive impact. It is important to understand how support systems and care services can deliver person-centered care in pre-symptomatic HD. Given the sessions’ consensual positive impact, we recommend other centers consider offering tailored support to people living in this stage.

Updates from the Ongoing PROOF-HD Phase 3 Study: Pridopidine’s Outcome On Function in Huntington’s Disease (PROOF)

Ralf Reilmann†, Andrew Feigin‡, Sandra Kostyk‡, Anne Rosser§, Michal Geva‡, Yael Cohen‡, Noga Gershoni-Emek §, Munish Mehra †, Michael R. Hayden†,‡

1George-Huntington-Institut, Muenster, Germany
2NYU Langone Health, Marlene and Paolo Fresco Institute for Parkinson’s and Movement Disorders, NY, USA
3The Ohio State University, College of Medicine, Columbus, Ohio, USA
4University of Cardiff, Wales, UK
5Prilenia Therapeutics, Israel
6Tigermed, Gaithersburg, MD, USA
7CMMT, University of British Columbia, Vancouver, Canada

Background: Pridopidine is an oral, well-tolerated drug candidate currently being evaluated in the global PROOF-HD PH3 trial for its effect on Total Functional Capacity (TFC) in early-stage HD. At 45 mg twice daily, the dose evaluated in PROOF-HD, pridopidine selectively and robustly activates the Sigma-1 Receptor, which modulates cellular processes impaired in HD. TFC is a validated, regulatory-accepted measure of clinical progression. In the PRIDE-HD trial, pridopidine 45 mg twice daily showed a beneficial effect vs. placebo on maintenance of TFC at week 52 (Δ0.87, p=0.0032). This effect is driven by early HD patients (TFC 7-13) (Δ1.16, p=0.0003). Responder analysis shows that
Abstracts

S26

Results: 763 patients with LoHD (median age: 70y; 56.5% female) were matched to 1,526 controls; 1,073 patients with AoHD (median age: 50y; 55.1% female) were matched to 2,146 controls. 67.4% of patients with LoHD and 49.8% of patients with AoHD had middle- or late-stage disease. Patients with LoHD or AoHD had a significantly higher probability of HCU across all medical service categories compared with controls. Compared with patients with AoHD, patients with LoHD had a similar probability of hospitalizations, and long-term care/nursing home, skilled nursing facility, and emergency room visits, but lower probability of physician office visits.

Conclusions: Patients with LoHD and AoHD have similar HCU burdens, which are significantly higher compared with controls.

Healthcare Utilization in Individuals with Late-Onset Versus Adult-Onset Huntington’s Disease

Jamie T. Ta*,1, Tu My To1, Anisha M. Patel1, Ibrahim M. Abbass1, Stella Arndorfer2, and Rita Gandhy1

1Genentech Inc., South San Francisco, CA, USA
2Genesis Research, Hoboken, NJ, USA

Background: Late-onset Huntington’s disease (LoHD) can occur in patients (pts) aged ≥60 years, but little is known about the relative burden of LoHD compared with adult-onset HD (AoHD).

Objectives: Assess healthcare utilization (HCU) among patients with LoHD versus AoHD and controls.

Methods: This retrospective cohort study used the IBM® MarketScan Commercial and Medicare Supplemental databases to identify patients with newly diagnosed HD, defined as having ≥1 HD diagnosis (ICD-9-CM: 333.4; ICD-10-CM: G10) between 2009-2017, aged ≥21 years at first HD diagnosis (index date) and with no HD claims for 12 months pre-index. Patients with HD aged 21-59 years were identified as having AoHD; ≥60 years were LoHD. Patients without HD (controls) were exact, and propensity score matched 2:1 to patients with HD. Multivariable logistic regression models estimated predicted probabilities for 12-month all-cause HCU among patients with LoHD, AoHD, and controls.

Young People’s Attitudes Towards Receiving Information About the Roche and Wave Life Trials

Bonnie L. Hennig-Trestman*, Beth Ann Griffin, Misty Daniel, Matthew Ellison, Marina Papoutsi, Mustafa Mehkary, Lauren Byrne, and Hayley Hubberstey

Huntington’s Disease Youth Organization (HDYO), Roanoke, VA, USA (all authors)

Background: To date, there have been very few disease-modifying clinical trials targeting Huntington’s disease (HD). Recently two pharmaceutical companies have tested promising drug molecules in hopes of finding treatments. In March 2021, based on recommendations from independent monitoring boards, drug dosing for each of the two trials was halted. Immediately, the HD scientific community arranged informational webinars to the public.

Objectives: This study seeks to examine young people’s attitudes toward receiving information about the closure of the studies from HD organizations.

Methods: Through social media (specifically Facebook) HD Youth Organization (HDYO) asked people (<35 years old) to share attitudes about the information they received. Once an individual responded affirmatively, they were connected to a brief online survey. The three questions asked were: (1) did they receive enough information about the trials; (2) did they receive adequate support following the cancellation of the dosing for the clinical
Abstracts

S27

Current HD Healthcare Capacity and Anticipated Gaps for Intrathecal Disease-Modifying Therapy Provision in Canada

Blair R. Leavitt*,1, Angèle Bénard2, Sylvain Chouinard1, Nathalie Budd4, Jennifer W. Wu1, and Kerrie Schoffer1

1University of British Columbia, Vancouver, British Columbia, Canada
2Huntington Society of Canada, Waterloo, Ontario, Canada
3Université de Montréal, Montréal, Québec, Canada
4Hoffmann-La Roche Ltd., Basel, Switzerland
5Dalhousie University, Halifax, Nova Scotia, Canada

Background: Modes of administering disease-modifying therapies (DMTs) for Huntington’s disease (HD) have raised concerns about healthcare capacity, especially in the publicly funded and geographically vast Canadian healthcare system.

Objectives: To assess the gap between current and future healthcare capacity required in the context of an approved DMT for manifest HD.

Methods: Data were collected via online survey (11/11/2020-18/01/2021) of 16 HD clinic neurologists and 16 social workers. Follow-up phone interviews were conducted with neurologists. The surveys and interviews evaluated resources, infrastructure, networks, and barriers to performing intrathecal (IT) infusions. To model future capacity, survey data and clinical trial protocols were used.

Results: The 15 responding HD clinics, who manage the majority of Canadian HD patients (mean: 146 patients/clinic), lack equitable access to multidisciplinary teams (MDTs; range: 2-35 members); only 47% have onsite nursing support. HD clinic neurologists (n=15) and social workers (n=16) are the most common MDT members, providing an average of 2.7 and 28.0 hours/week of HD patient care, respectively. According to modeling, only 15% of patients meeting IT DMT eligibility are currently seen in HD clinics. Modeling shows a 94% gap in capacity to treat following IT DMT introduction and uptake.

Conclusions: Current low and inequitable MDT resourcing in Canadian HD clinics would be further stretched following the approval of a DMT. Staffing is a critical bottleneck to the expansion of HD healthcare capacity.

Effects of Long-Term Deutetrabenazine Treatment on Psychiatric and Cognitive Safety Outcomes in Chorea Associated with Huntington’s Disease

Samuel Frank*,1, David Stamler2, Elise Kayson3, Christina Vaughanan, Jody Goldstein4, Jacquelyn Whaley5, Nicholas Gross6, Juha-Matti Savola7, and Mark Forrest Gordon7 on behalf of the Huntington Study Group ARC-HD Investigators

1Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, Massachusetts, USA
2Teva Pharmaceuticals, La Jolla, California, USA
3University of Rochester, Rochester, New York, USA
4University of Colorado, Denver, Colorado, USA
5Huntington Study Group, Rochester, New York, USA
6Center for Health + Technology, University of Rochester, Rochester, New York, USA
7Teva Pharmaceuticals, West Chester, Pennsylvania, USA
8Teva Pharmaceuticals, Basel, Switzerland

Background: Huntington’s disease (HD) is characterized by motor impairment, decline in cognitive function, and behavioral-emotional disturbances. Deutetrabenazine, a VMAT2 inhibitor,
is FDA-approved for the treatment of chorea in HD. Deutetrabenazine significantly improved chorea with favorable safety in a 12-week pivotal trial (First-HD) and the long-term open-label extension study (ARC-HD).

**Objectives:** To evaluate changes in long-term assessments of psychiatric and cognitive safety with deutetrabenazine in patients with HD chorea.

**Methods:** The three-year ARC-HD study enrolled patients who completed First-HD (Rollover) and patients who converted overnight from a stable dose of tetrabenazine (Switch). Psychiatric and cognitive safety were assessed by the following: Hospital Anxiety and Depression Scale (HADS), Montreal Cognitive Assessment (MoCA), Epworth Sleepiness Scale (ESS), and Columbia Suicide Severity Rating Scale (C-SSRS).

**Results:** ARC-HD included 119 patients (Rollover, n=82; Switch, n=37). Mean±SD change from baseline to Week 145 in the Rollover and Switch cohorts, respectively, were HADS anxiety (1.7±3.68 and –0.8±5.76); HADS depression (3.2±4.76 and 0.3±4.98); MoCA (–2.3±4.01 and –1.8±4.26); and ESS (2.2±5.13 and 1.7±7.25). For HADS and ESS, higher score and positive change indicate greater impairment. For MoCA, lower score and negative change indicate greater impairment. Prior to treatment, C-SSRS results for Rollover and Switch cohorts, respectively, were suicidal ideation (15.9% and 10.8%) and suicidal behavior (1.2% and 0%). During the treatment period, C-SSRS results for Rollover and Switch, respectively, were suicidal ideation (13.6% and 10.8%) and suicidal behavior (3.7% and 2.7%).

**Conclusions:** Over three years, deutetrabenazine was generally well tolerated with respect to scales typically used to assess anxiety, depression, cognition, and sleepiness.

**Effects of Long-Term Deutetrabenazine Treatment on Motor Safety Outcomes in Chorea Associated with Huntington’s Disease**

Samuel Frank*1, David Stamler2, Elise Kayson1, Christina Vaughan1, Jody Goldstein1, Jacquelyn Whaley6, Nicholas Gross7, Juha-Matti Savola8, and Mark Forrest Gordon7 on behalf of the Huntington Study Group ARC-HD Investigators

Background: Chorea is a hallmark motor symptom of Huntington’s disease (HD). Deutetrabenazine, a VMAT2 inhibitor, is FDA-approved for the treatment of chorea in HD. Deutetrabenazine treatment significantly reduced chorea with a favorable safety profile in the 12-week pivotal trial First-HD and the long-term open-label extension study ARC-HD.

**Objectives:** To evaluate the long-term effects of deutetrabenazine on motor measures in patients with HD chorea.

**Methods:** ARC-HD, a three-year study, included patients who completed First-HD (Rollover) and patients who converted overnight from a stable dose of tetrabenazine (Switch). Motor measures were assessed based on the following safety scales: Unified Huntington’s Disease Rating Scale (UHDRS) parkinsonism subscore, Unified Parkinson’s Disease Rating Scale (UPDRS) dysarthria item, Swallowing Disturbance Questionnaire (SDQ), and Barnes Akathisia Rating Scale (BARS).

**Results:** ARC-HD enrolled 119 patients (Rollover, n=82; Switch, n=37). Mean±SD change from baseline to Week 145 for patients in the Rollover and Switch cohorts, respectively, for each score were: UHDRS parkinsonism (3.6±4.57 and 2.4±5.39), UPDRS dysarthria (0.7±0.68 and 0.6±0.98), SDQ (3.8±5.88 and 6.6±10.86), BARS summary (–0.2±1.25 and –0.2±2.81), and BARS global (–0.1±0.70 and 0.1±1.51)(for these metrics, higher score and positive change indicate greater impairment).

**Conclusions:** Over three years, deutetrabenazine was generally well tolerated with respect to motor safety measures in patients with HD chorea, and no safety concerns emerged with long-term exposure. The increased scores on measures of disease were not out of proportion to the expected progression of HD.
Assessing the State of Care for Huntington’s Disease (HD) in the United States: Results from a Survey of Practices Treating HD Patients

Lauren Seeberger*1, Jody Corey-Bloom2, Michael O’Brien3, Peggy Chen4, Beth Ann Griffin5, Danielle Schlang6, and Diana Slowiejko7

1University of Colorado, Aurora, CO, USA (on behalf of the Huntington Study Group)
2University of California, San Diego, San Diego, CA, USA
3Huntington Study Group, Rochester, NY, USA
4RAND Health Care, Santa Monica, CA, USA
5Genentech, Inc., South San Francisco, CA, USA

Background: No study to date has thoroughly examined U.S. HD care delivery in a variety of clinic settings by HD specialists and non-specialists.

Objectives: To obtain a clearer understanding of current care structure and delivery of care through a survey of representative U.S. physicians treating HD patients.

Methods: We designed and fielded a survey of 40 closed-ended evaluative questions and one open-ended item to a sample of 339 U.S. practices; unique to this survey was the inclusion of non-specialists.

Results: Responses were received from 156 practices (overall response rate 46.02%), with 52.6% from academic sites, 35.3% from private practices, and 12.2% from the VA. More than half (63.5%) of the practice leads were movement disorder trained or directors of HDSA Centers of Excellence, and 58.3% had an HD or multidisciplinary care clinic. However, 48.7% of the practices saw 1-25 HD patients; 28.2% saw 26-100 HD patients; and 23.1% saw over 100 HD patients annually. Most practices (>69%) reported having difficulty providing social work, genetic counseling, care coordination, and psychologists/psychiatrists. Increased HD practice size was associated with higher rates of pre-visit screenings, care navigator/care coordinators, routine monitoring of weight, and provision of genetic counseling by genetic counselors.

Conclusions: Not surprisingly, we found that HD care was inconsistently applied across the U.S. Practices led by neurologists trained in movement disorders and higher HD volume practices tended to be better equipped to provide multi-disciplinary staffing and procedures as compared to those with fewer numbers of HD patients.

Broadening the Scope of Understanding Huntington’s Disease Through the Assessment of the Impact on Social Domains in Relation to Disease Progression

T. Gardner*1, A. Maur1, N. Layton2, N. Brusco2, and L. Callaway2

1Huntington’s Victoria, Hawthorne, Victoria, Australia
2Monash University, Melbourne, Australia

Background: Historically, the impacts of Huntington’s disease (HD) have been recognized through the prism of a medical model. Huntington’s Victoria (HV) has been in a unique position, as a direct service community provider, to also identify impacts of HD from a psychosocial perspective. Consequently, HV developed a Social Impact Measurement (SIM) Tool in collaboration with the community to enable a consistent and responsive approach to assessing and addressing unmet needs.

Objectives: To verify the social impact domains with the purpose of including them in an overall assessment tool.

Methods: Evaluation of the HV SIM via two-staged consumer engagement including: (1) mapping of the HV SIM domains against inter/national outcome frameworks and (2) verification of the HV SIM through a formalized process with direct input from consumers via interviews with clinical experts and HD community (n=11); oversight of a steering committee of community representatives with lived experience of HD; and a focus group broadly represented by persons with HD (gene positive and diagnosed), families, service providers, and peak bodies (n=28) to verify outcomes from the interviews.

Results: The validity of the HV SIM was confirmed with respect to lived experience, as well as compared with World Health Organization and COAG outcome frameworks. The two overarching themes that categorize these domains include risks and safety (including housing and economic sustainability) and social inclusion (health and symptom management, physical wellbeing, emotional wellbeing, and building resilient relationships).

Conclusions: Thus far, there has been limited understanding of the impacts of HD across the social domains. The completion of a co-designed HV SIM and its conversion into a measurement tool provides...
a comprehensive framework by which to assess and respond to unmet needs allowing an informed approach to care coordination, service delivery, and evaluation of effectiveness.

48

Proof-of-Concept Study Testing SOM3355 in the Treatment of Chorea Symptoms in Huntington’s Disease

J. Gamez1, M. Calopa2, E. Muñoz3, A. Ferré*, O. Huertas4, K. McAllister5, N. Reig4, C. Scart-Grès4, R. Insa4, and J. Kulisevsky6

1Neurology Department, GMA Clinics, Universitat Autònoma de Barcelona, Barcelona, Spain
2Movement Disorders Unit, Neurology Department, Hospital Universitari de Bellvitge, L’Hospitalet de Llobregat, Barcelona, Spain
3Parkinson’s Disease and Movement Disorders Unit, Neurology Service, Institut Clínic de Neurociències, Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain
4SOM Innovation Biotech SA, Barcelona, Spain
5Neurenable GmbH, Basel, Switzerland
6Movement Disorders Unit, Neurology Department, Hospital de la Santa Creu i Sant Pau, Institut d’Investigació Biomèdica Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

Background: SOM3355 (bevantolol), a β1-adrenoceptor blocker used in hypertension, was identified as a vesicular monoamine transporter type 2 (VMAT2) inhibitor by artificial intelligence screening, and then was selected by in vitro functional studies as the best candidate to be repositioned for treatment of dyskinetic movement disorders, such as chorea in Huntington’s disease (HD).

Objectives: (1) To continue to provide responsive service to a community that is reliant on regular contact from the organization. (2) To prevent staff burnout due to the added strain of the COVID-19 pandemic in order to continue to provide responsive service to the community.

Methods: (1) Provide a six-week online program to the staffing group to support their adaptation to the COVID-19 restrictions. (2) Manage technology and update information to support the adaptation of the COVID-19 restrictions on service provision.

Results: Staff members were provided with a tailored psychosocial support program to assist in managing their own adaptation to COVID-19. Service provision was able to be continued despite the limitation of no face-to-face practice. Technology-based areas of the organization were improved and utilized to continue supporting the community moving forward.

Conclusions: Due to the established collaborative and trusting working relationship between HV and its community, the organization was able to effectively adopt appropriate technology in a short period of time. This added value and enabled the continuity of service delivery through the COVID-19 pandemic. The Huntington’s Victoria staff members were also supported to perform their roles while experiencing the impacts of the pandemic through the availability of additional psychological support via a tailored program.

49

Providing a Responsive and Updated Service to the HD Community During the COVID-19 Pandemic

T. Gardner*, J. Southern*, and A. Maur

Huntington’s Victoria, Hawthorne, Victoria, Australia (all authors)

Background: Huntington’s Victoria has always been a community driven organization, centralized around face-to-face delivery. The COVID-19 pandemic required HV to acknowledge the limitations of service delivery by altering the way that they responded to the community and their needs. This also involved the needs of the staffing group and the internal workings of the organization.

Objectives: (1) To continue to provide responsive service to a community that is reliant on regular contact from the organization. (2) To prevent staff burnout due to the added strain of the COVID-19 pandemic in order to continue to provide responsive service to the community.

Methods: (1) Provide a six-week online program to the staffing group to support their adaptation to the COVID-19 restrictions. (2) Manage technology and update information to support the adaptation of the COVID-19 restrictions on service provision.

Results: Staff members were provided with a tailored psychosocial support program to assist in managing their own adaptation to COVID-19. Service provision was able to be continued despite the limitation of no face-to-face practice. Technology-based areas of the organization were improved and utilized to continue supporting the community moving forward.

Conclusions: Due to the established collaborative and trusting working relationship between HV and its community, the organization was able to effectively adopt appropriate technology in a short period of time. This added value and enabled the continuity of service delivery through the COVID-19 pandemic. The Huntington’s Victoria staff members were also supported to perform their roles while experiencing the impacts of the pandemic through the availability of additional psychological support via a tailored program.
Abstracts

S31

optimized to minimize efflux by P-glycoprotein and other drug efflux pumps. The resulting compounds effectively lower huntingtin evenly throughout all regions of the brain and in the periphery of HD mice. **Objectives:** We aimed to develop an orally bioavailable, brain-penetrating, small molecule HTT-lowering splicing modifier for the treatment of HD, which would avoid the need for an invasive and potentially unsafe procedure to administer the drug uniformly to key affected areas of the brain. **Methods:** Here, we describe the chemical optimization campaign to identify HTT-lowering small molecule splicing modifiers with favorable physicochemical properties, demonstrating optimal central nervous system and peripheral HTT lowering. **Results:** We identified orally bioavailable compounds with reduced efflux that demonstrated dose-dependent and equitable lowering of HTT within the brain (including the cortex and striatum) and peripheral tissues of HD mice. **Conclusions:** These results underscore the potential of oral small molecules with reduced efflux as HTT-lowering therapeutics for HD, as they can be administered safely and conveniently, without invasive procedures. This lead optimization process led to the identification and advancement of PTC518 into the clinical development phase.

51

**Small Molecules as Oral Therapeutics in Patients with Huntington’s Disease (HD): Providing Uniform Drug Distribution and Lowering of Huntingtin Protein (HTT)**

Anuradha Bhattacharyya*, Suresh Babu, Jana Narasimhan, Matthew Woll, Minakshi Jani, Nicole Risher, Shirley Yeh, Yaofeng Cheng, Nadiya Sydorenko, Young-Choon Moon, and Stuart Peltz

PTC Therapeutics, Inc., South Plainfield, NJ, USA (all authors)

**Background:** Reducing HTT levels in animal models alleviates motor and neuropathological abnormalities, supporting HTT-lowering as a therapeutic approach. An orally bioavailable, brain-penetrating small molecule that reduces the mutant HTT toxic burden uniformly throughout all the critical areas of an HD brain will be extremely beneficial. The need for a disease-modifying HTT-lowering therapeutic has further intensified with the recent developmental cessation of some antisense oligonucleotides (ASO). While the exact reasons for cessation are being investigated, it appears safety issues (e.g., hydrocephalus) may represent a class-effect associated with administering ASOs, which do not cross the blood brain barrier and do not distribute evenly throughout the brain. Here, we describe the chemical optimization of a class of small molecule splicing modifiers, which lower huntingtin in the brain and periphery of HD mice. The orally bioavailable molecules were optimized to minimize efflux by P-glycoprotein and other drug efflux pumps. The resulting compounds effectively lower huntingtin evenly throughout all regions of the brain and in the periphery of HD mice. **Objectives:** We aimed to develop an orally bioavailable, brain-penetrating, small molecule HTT-lowering splicing modifier for the treatment of HD, which would avoid the need for an invasive and potentially unsafe procedure to administer the drug uniformly to key affected areas of the brain. **Methods:** Here, we describe the chemical optimization campaign to identify HTT-lowering small molecule splicing modifiers with favorable physicochemical properties, demonstrating optimal central nervous system and peripheral HTT lowering. **Results:** We identified orally bioavailable compounds with reduced efflux that demonstrated dose-dependent and equitable lowering of HTT within the brain (including the cortex and striatum) and peripheral tissues of HD mice. **Conclusions:** These results underscore the potential of oral small molecules with reduced efflux as HTT-lowering therapeutics for HD, as they can be administered safely and conveniently, without invasive procedures. This lead optimization process led to the identification and advancement of PTC518 into the clinical development phase.

A New Deep-Learning Model for Putamen Segmentation

Jack Weatheritt*, Iman Gidado1, Marina Papoutsi1, Richard Joules1, and Robin Wolz1,2

1IXICO PLC, London, UK
2Imperial College London, London, UK

**Background:** Volume change over time of the putamen is an important biomarker in Huntington’s disease (HD). Putamen volume is used to define transition from stage 0 to disease stage 1 according to the recent HD integrated staging system. In addition, the putamen is used as an injection site in recent gene therapies. Consequently, it is important to provide accurate segmentations of the putamen to be used in clinical trials both for eligibility and efficacy measurement. However, the putamen is very challenging to segment for both manual and automated methodologies due to unclear region
Racial Differences in Indices of Disease Burden and Progression in Huntington’s Disease

Elicia C. Osigwe, Danielle A. Buchanan*, Anna C. Pfalzer, and Daniel O. Claassen
Vanderbilt University Medical Center, Nashville, TN, USA (all authors)

Background: Huntington’s disease (HD) predominantly affects those of European descent, which limits investigations into potential racial disparities in disease manifestation, management, and progression.

Methods: Using the Enroll-HD dataset PDS5, we examined differences in baseline clinical characteristics in HD patients by race. We randomly selected a cohort of white patients with a sample size similar to other races: Black, Hispanic, Asian, Multiracial, and “Other.” We examined differences in baseline characteristics such as age, gender, education level (ISCED), and CAG repeat length, as well as cognitive measures (Symbol Digit Modality Test [SDMT], Stroop Word Reading [SWR]), UHDRS motor score, and total functional capacity (TFC). Two metrics of disease burden were calculated: CAG-Age Related product (CAP) score and the composite Unified Huntington’s Disease Rating Scale (cUHDRS). We examined differences in disease progression using the change in cUHDRS.

Results: Black participants were younger in age (46.22±1.30) at baseline than white and “Other” participants and had the highest CAG-repeats (45.99±0.48) and motor scores (38.76±2.27). Not surprisingly, Black participants had a significantly higher CAP (529.5±13.2) and lower cUHDRS (6.943±0.53) than all other races, indicative of greater disease burden at baseline. Interestingly, Multiracial participants had the best performance on the SWR (74.83±2.03) and SDMT (37.96±1.36) cognitive assessments; however, there were no significant differences in education level between the races. Multiracial participants also scored the highest on TFC (10.70±0.24), while Black participants scored the lowest (8.216±0.35). Native American, Other, and Multiracial participants had a significantly slower change in disease progression compared to White, Black, Asian, and Hispanic participants as measured by the change in cUHDRS.
**Conclusions:** Black participants have a significantly more advanced disease profile at baseline compared to several other races. The cause of these baseline differences remains unknown, although it appears to be independent of education level. It is noteworthy that we observed significant differences in motor manifestation prior to deficiencies in cognitive performance in several races, further highlighting the complexity in disease manifestation in HD. Future studies should begin to explore potential causes of these racial differences in baseline and disease progression. These studies would most likely include an investigation into socioeconomic status and psychiatric evaluations.

**Results:** We found increased plasma levels of C1q and multiple complement components, as well as an increased levels of NfL in both plasma and CSF of R6/2 mice. There was a significant positive correlation between CSF NfL levels and plasma C1q, suggesting a potential role of the classical complement cascade in neurodegeneration. Treatment of animals with anti-C1q fully blocked C1q in the plasma, normalized levels of complement components, significantly reduced CSF NfL levels, improved motor behavior, and increased R6/2 mouse survival.

**Conclusions:** This study suggests that inhibiting C1q protects against neurodegeneration in R6/2 mice and that C1q is a potential pharmacological target in HD. A Phase 2 study of ANX005 anti-C1q therapy in HD patients is ongoing (clinicaltrials.gov NCT04514367).

---

**Pharmacologic Inhibition of the Classical Complement Pathway Enhances Neuronal Function and HD R6/2 Mouse Survival**


*Annexon Biosciences, South San Francisco, CA, USA (all authors)*

**Background:** Huntington’s disease (HD) is a neurodegenerative disorder caused by expansion of CAG repeats in the Huntingtin (HTT) gene. Increased expression of early classical complement components has been observed in striatal tissue from HD patients, and C1q has been implicated in neurodegeneration in HD mouse models.

**Objectives:** To examine complement expression, neurodegeneration, and the potential therapeutic benefit of classical complement inhibition in an HD animal model.

**Methods:** We used the R6/2 transgenic mouse model of HD expressing a ~120 CAG expansion and measured classical complement components in the plasma and cerebral spinal fluid (CSF) of transgenic vs. wild type mice. We measured the levels of Neurofilament Light Chain (NfL) as a biomarker of neurodegeneration. To test the role of the classical complement pathway in neurodegeneration, we pharmacologically blocked C1q activity with intraperitoneal administration of an inhibitory antibody (ANX-M1), and assessed NfL, motor behavioral function, and animal survival.

---

**Defining Clinical Progression of Juvenile-Onset Huntington’s Disease: An Enroll-HD Analysis**

Sophia Nopoulos*, Erin Reasoner, Amy Ogilvie, and Jordan L. Schultz

*The University of Iowa, Iowa City, IA, USA (all authors)*

**Background:** Patients with juvenile-onset Huntington’s disease (JOHD) have a unique, hypokinetic presentation compared to patients with adult-onset HD (AOHD) who present with hyperkinetic symptoms. Patients with AOHD sometimes experience hypokinetic symptoms in the late stages of the disease. Therefore, it is unclear if the unique phenotype seen in JOHD is caused by novel pathologic mechanisms or if these patients reach a hypokinetic stage much earlier in the disease. We leveraged the Enroll-HD database to compare motor patterns of JOHD to patients with AOHD and early-onset HD (EOHD).

**Methods:** Patients with HD were split into those with JOHD (CAG ≥ 60 and age of motor onset (AMO) ≤ 21 years), EOHD (CAG > 45 and AMO between 21 and 30), or AOHD (CAG ≤ 45 and AMO > 30). We used non-linear mixed-effects regression models to compare the trajectory of the total motor score (TMS) between groups controlling for age, CAG, and sex. Similar models were constructed to compare trajectories for all subscales of the UHDRS across groups.

**Results:** TMS progression was fastest in the JOHD group, followed by the EOHD and AOHD groups.
At diagnosis, chorea was the prominent symptom in all three groups. However, chorea decreased over time in the JOHD group while hypokinetic symptoms increased at a significantly faster rate compared to the EOHD and AOHD groups.

**Conclusions:** The unique motor symptoms in JOHD most likely are not the result of novel neuropathologic mechanisms; rather, they likely represent the accelerated trajectory of motor symptoms that start hyperkinetic and then progress to hypokinetic.

---

## Behavioral Features of Huntington’s Disease and Their Relationship with Striatal Volume in Children and Adolescents

Erin E. Reasoner¹, Ellen van der Plas¹, Hend M. Al-Kaylani*¹, Douglas R. Langbehn¹, Amy L. Conrad², Jordan Schultz¹, Eric Epping¹, and Peggy C. Nopoulos¹,²,³

¹Department of Psychiatry, University of Iowa Hospital and Clinics, Iowa City, IA, USA

²Stead Family Children’s Hospital at the University of Iowa, Iowa City, IA, USA

³Department of Neurology, University of Iowa Hospital and Clinics, Iowa City, IA, USA

**Background:** Behavioral changes are a prominent feature of Huntington’s disease (HD), usually manifesting before motor onset. Atypical striatal development has been reported in mutant huntingtin (mHTT) carriers, but little is known about how this may affect the development of behavioral features of HD.

**Objectives:** Using data from the Kids-HD study, we compared neuropsychiatric symptoms between child and adolescent mHTT carriers and peers who did not inherit mHTT. We also evaluated the relationship between neuropsychiatric traits and striatal development.

**Methods:** Children and adolescents (6-18 years old) were recruited from families affected by HD. Following an accelerated longitudinal design, the sample included 59 gene-expanded (GE) individuals and 91 gene-non-expanded (GNE) individuals. The Pediatric Behavior Scale (PBS) and Behavior Rating Inventory of Executive Function (BRIEF) assessed neuropsychiatric traits. Striatal volumes were extracted from 3T neuro-anatomical images. Multivariable linear regression models evaluated the impact of group, age, and age-dependent change in striatal volume on neuropsychiatric symptoms.

**Results:** Depression/anxiety was higher in the GNE group compared to the GE group (Estimate = 4.26, t(129) = 2.380, FDR = 0.075). The age-dependent change in striatal volume predicted depression scores (Estimate = 0.429, 95% CI 0.15:0.71, p = 0.0029). Increased depression was associated with smaller striatal volume in younger children; inversely, increased depression was associated with larger striatal volume in adolescents.

**Conclusions:** Lower depression scores were associated with age-dependent loss of striatal volume. Differences in striatal development between GNE and GE may be associated with reduced risk of depression/anxiety in child and adolescent mHTT carriers.

---

## Chorea Characteristics and Treatment Pattern in Patients with Huntington Disease: Current Data from Enroll-HD

Erin E. Furr-Stimming¹, Daniel O. Claassen², Ginny P. Sen*³, Mallory Farrar¹, Ericha Franey³, Chuck Yonan¹, and Dietrich Haubenberger³

¹The University of Texas Health Science Center at Houston, Houston, TX, USA

²Vanderbilt University Medical Center, Nashville, TN, USA

³Neurocrine Biosciences, Inc., San Diego, CA, USA

**Background:** Enroll-HD is a worldwide, prospective, observational study of individuals who have (or are at-risk for) Huntington disease (HD).

**Objectives:** To determine chorea characteristics and treatment patterns using Enroll-HD Periodic Dataset 5.0.

**Methods:** Analyses included North American patients (≥18 years) with Unified Huntington Disease Rating Scale (UHDRS) diagnostic confidence level 4 at each study visit. Chorea was defined as UHDRS Total Maximal Chorea ≥2, and medications for chorea (as indicated in the Enroll-HD database) were categorized as follows: vesicular monoamine transporter 2 inhibitor alone (VMAT2), antipsychotics alone (AP), medication other than VMAT2 or AP (Other), and 2+ different medications from previous 3 categories (Combination).

**Results:** Chorea was indicated in 96.8% (2507/2590) of eligible patients and 96.5% (6678/6920) of visits.
36.2% (907/2507) of patients with chorea were prescribed an anti-chorea medication at any visit, with VMAT2 being the most common first-line treatment (43.4%), followed by AP (24.0%), Other (16.2%), and Combination (3.5%). Average treatment duration ranged from 28.8 (VMAT2) to 41.0 (AP) months. 84.3% and 77.2% of patients remained on first-line VMAT2 or AP, respectively, versus 52.7% for Other. Among patients with a treatment change, approximately one-half switched to combination therapy and one-third discontinued treatment for >90 days (mean gap 1–2 years). 7.1% (64/907) of patients had ≥3 lines of treatment.

**Conclusions:** Although chorea was indicated in most HD patients at most visits, only 36.2% received a medication to address chorea. Most patients on an anti-chorea medication tended to stay on their initially prescribed therapy, most commonly VMAT2 or AP.

---

**58**

**A Model Incorporating Levels of Complement Activation More Accurately Predicts Huntington’s Disease Progression Than Neurofilament Light**

Poojan Suri*, Ann Mongan†, Yaisa Andrews-Zwillling†, Nia Rahman-Khan Arana†, Julian Low†, Sethu Sankaranarayanan†, Lauren Byrne‡, Ping Lin‡, Henk-André Kroon*, Ted Yednock†, Edward Wild‡, and Ellen Cahir-McFarland†

1Annexon Biosciences Inc., South San Francisco, CA, USA
2Huntington’s Disease Centre, University College London, Institute of Neurology, London, UK

**Background:** There is an unmet need to identify mediators of neuronal dysfunction in Huntington’s disease (HD) and to characterize natural history so that therapeutic effects can be accurately assessed. Existing literature has shown that the classical complement cascade is involved in mediating synaptic pruning during early neuron development, and there is growing evidence that aberrant activation of this pathway leads to neuronal damage in neurodegenerative disorders like HD.
Objective: This study aims to understand involvement of the complement cascade in HD and quantify contribution of complement activation towards disease progression.

Methods: Discovery and tested cohorts are patients at University College London (n=60) and Clarity (n=100), respectively. Complement proteins and NfL were measured using in-house ELISA and Uman kit, respectively. A machine learning model was developed to assess contribution of complement activation towards cUHDRS. Accuracy and improvement of this model over linear models of NfL and age were determined by root mean square error.

Results: We were able to more accurately model disease disability (cUHDRS) using a combination of NfL, age, and level of complement involvement than predicted by NfL (p-val = 2*10-15) or NfL+age (p-val = 3*10-12). The improvement is particularly significant in manifest HD when rate of NfL increases plateaus, but disease progression accelerates. CSF C4a level is significantly higher in HD patients relative to healthy controls and increases as disease progresses. This association is significant after accounting for age-related effect (p-val < 0.01).

Conclusions: Positive correlation of C4a with NfL (r=0.6, p<0.01) suggests that activation of classical complement may be linked to neuronal cell death. Together, this model suggests a role of complement activation in HD progression and allows for a more quantitative assessment when evaluating therapeutic effect.

Cortical Features in Child and Adolescent Carriers of Mutant Huntingtin (mHTT)

Erin E. Reasoner*, Ellen van der Plas1, Douglas R. Langbehn1, Amy L. Conrad2, Timothy R. Koscik1, Eric A. Epping1, Vincent A. Magnotta3, and Peggy C. Nopoulos1,4

1Department of Psychiatry, University of Iowa Hospital and Clinics, Iowa City, IA, USA
2Stead Family Department of Pediatrics, University of Iowa Hospital and Clinics, Iowa City, IA, USA
3Department of Radiology, University of Iowa Hospital and Clinics, Iowa City, IA, USA
4Department of Neurology, University of Iowa Hospital and Clinics, Iowa City, IA, USA

Background: Molecular studies provide evidence that mutant huntingtin (mHTT) affects cortical neurogenesis; however, developmental trajectories of the cortex have not been evaluated in young individuals at risk for HD.

Objectives: To compare cortical development in child and adolescent carriers and non-carriers of mHTT.

Methods: Children and adolescents (6-18 years) participated in the Kids-HD study, where mHTT carrier status was determined with the purpose of classifying participants as gene expanded (GE) and gene non-expanded (GNE). All participants were estimated to be over 20 years from motor onset. Cortical features were extracted from 3T neuroimaging using FreeSurfer. Nonlinear mixed-effects models were conducted to determine if age, group, and CAG repeat were associated with cortical morphology.

Results: Age-related changes in cortical morphology were similar across groups, and expanded CAG repeat was not significantly associated with cortical features.

Conclusions: While we have previously demonstrated that striatal development is markedly different in GE and GNE individuals, developmental change of the cortex appears normal among children and adolescents at risk for HD.

Huntington Disease: Proposal for Care Recommendations in the Premanifest Years

Elizabeth McCusker1,2, Florence Ching-fen Chang*, Nicholas Murray3, and Clement Loy1,2

1Huntington Disease Unit, Westmead Hospital, Darcy and Hawkesbury Road, Westmead, New South Wales, Australia
2Sydney Medical School, Westmead Hospital, Darcy and Hawkesbury Road, Westmead, New South Wales, Australia

Background: Environmental factors and genetic modifiers may influence the Huntington’s disease (HD) phenotype and age of motor onset by 30% or more.

Objectives: We would like to formulate lifestyle recommendations to delay HD onset in the premani-
fest patient population by systematically reviewing the literature.

**Methods:** A comprehensive and structured search in PubMed following PRISMA protocol to identify human studies examining modifiable factors that influence HD onset and progression. Animal studies were excluded. MEDLINE, Google Scholar, and EMBASE Web of Science database were searched using keywords: “Huntington disease onset” and “risk factor,” “Huntington disease” and “phenoconversion,” and “Huntington disease “and” prevention.”

**Results:** Tobacco, illicit drugs, alcohol, co-existing HIV infections, passive lifestyles, higher daily caloric intakes, dairy products, and caffeine or caffeinated soda intakes were all associated with earlier age of HD onset. Treatment of hypertension with antihypertensive medication and maintaining higher cognitive engagement were associated with later age of onset. Higher level of education was associated with earlier onset age across motor, cognitive and psychiatric domains. Those with higher education levels had lower motor scores and higher cognitive test scores upon diagnosis, suggesting earlier symptom recognition.

**Conclusions:** Abstinence from tobacco and illicit drugs, safe levels of alcohol intake, avoiding HIV infection risks, excess daily caloric or caffeine intake, maintaining a physically and cognitively active lifestyle, and medical treatment of hypertension may delay age of HD onset. While further large prospective studies are needed, these findings should be included in care discussions.

61

“Man, This Isn’t Easy”: Exploring the Manifestation of Parentification Among Young Carers of a Parent with Huntington’s Disease

Bailey A. Hendricks*, Marie A. Bakitas1, J. Nicholas Dionne-Odom1, Emily Johnston4, Gwendolyn Childs1, and Melinda Kavanaugh2

1School of Nursing, University of Alabama at Birmingham, Birmingham, AL, USA
2Helen Bader School of Social Welfare, University of Wisconsin-Milwaukee, Milwaukee, WI, USA
3Center for Palliative and Supportive Care, University of Alabama at Birmingham, Birmingham, AL, USA
4Institute for Cancer Outcomes and Survivorship, University of Alabama at Birmingham, Birmingham, AL, USA

**Background:** Due to the progressive deterioration of motor, cognitive, and psychological function associated with Huntington’s disease (HD), children in the home may adopt a caregiving role. These young carers provide multifaceted, extended care without lessening of their typical responsibilities. In time this can result in parentification, a type of role reversal with bimodal outcomes.

**Objectives:** To explore the manifestation of parentification among young carers of persons with HD.

**Methods:** A secondary analysis of qualitative data from a parent study on the experiences of children who had a parent with HD was conducted. A directed content analysis of interview data guided by a literature-derived framework of parentification among young carers was utilized.

**Results:** The sample consisted of 28 self-identified young carers with a mean age of 16.6 who had been providing care for 1-3 years (53.6%) (25.4 hrs/week). Data analysis resulted in three main themes with subthemes: (1) being a young carer (feelings regarding the role, learning to be a caregiver, caregiver burden, coping), (2) dealing with it (school and friends, feeling unheard/alone, support system, personal growth), and (3) facing the uniqueness of being an HD caregiver (stigma and isolation, parent/child relationship changes, acknowledging end of life, genetic risk).

**Conclusions:** Being a young carer of a person with HD presents unique challenges; elements of parentification were evident in some, but not all carers. Exploring how parentification may manifest in the context of HD is important for guiding future policy, research, and support services.

62

“COVID-19 Impact on Genetic Counseling for Huntington’s Disease via Telehealth”

Wes Solem*, Debra Roter1, and Leila Jamal1

1Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
2National Human Genome Research Institute, Bethesda, MD, USA
3National Cancer Institute, Bethesda, MD, USA

**Background:** Traditionally, most Huntington’s disease genetic counseling (HDGC) has been provided in-person. During the COVID-19 pandemic, many genetic counselors (GCs) were forced to provide
Background: Biomarkers are needed to monitor disease progression, target engagement, and efficacy in Huntington’s disease (HD). Cerebrospinal fluid (CSF) is an ideal medium to research such biomarkers due to its proximity to the brain.

Objectives: To investigate the safety and feasibility of research lumbar punctures (LP) in HD.

Methods: U.S.-based GCs with 18 months or more experience providing HDGC (N=49) completed an electronic survey assessing the nature and extent of HD-TGC services offered and GC attitudes toward HD-TGC services. Purposively selected participants (n=17) also completed a semi-structured interview to explore these topics in greater detail.

Results: Preliminary survey results reflect that most GCs who provided HD-TGC indicated they would rather use TGC if in-person services require masks and physical distancing and believe HD-TGC should continue to be offered as an option. In interviews, examples of positive reflections discussed include increased convenience for patients and support companions. Some challenges discussed include impaired therapeutic connection and distracted patients.

Conclusions: The COVID-19 pandemic provided an unexpected opportunity to explore the utility of HD-TGC as an option. The majority of GCs indicated their comfort in providing HD-TGC grew over time, and they believed HD-TGC would continue to be provided post-COVID-19.

Safety and Feasibility of Research Lumbar Puncture in Huntington’s Disease: The HDClarity Cohort and Bioresource

Filipe B. Rodrigues¹, Gail Owen¹, Swati Sathe², Elena Pak², Dipinder Kaur², Anka G. Ehrhardt², Sherry Lifer², Jenny Townhill³, Katarzyna Schubert¹, Blair R. Leavitt⁴, Mark Guttman⁵, Jee Bang⁶, Jan Lewerenz², Jamie Levey²,³ (for the HDClarity Investigators), Cristina Sampao², and Edward J. Wild*¹

¹University College London, Huntington’s Disease Centre, UCL Queen Square Institute of Neurology, London, UK
²CHDI Management/CHDI Foundation, Princeton, NJ, USA
³Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
⁴Division of Neurology, Department of Medicine, University of Toronto, Toronto, ON, Canada
⁵Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background: HDGC via telehealth (HD-TGC). Little is known about GCs’ experiences of providing HD-TGC. To address this knowledge gap, we conducted a retrospective, mixed-methods study consisting of surveys and interviews with HD GCs.

Objectives: Our objectives were twofold: (1) to assess the nature and extent of HD-TGC services offered during COVID-19 restrictions and (2) to assess genetic counselors’ attitudes toward HD-TGC services and their perceptions of factors that favor or hinder effective HDGC using telehealth.

Methods: U.S.-based GCs with 18 months or more experience providing HDGC (N=49) completed an electronic survey assessing the nature and extent of HD-TGC services offered and GC attitudes toward HD-TGC services. Purposively selected participants (n=17) also completed a semi-structured interview to explore these topics in greater detail.

Results: Preliminary survey results reflect that most GCs who provided HD-TGC indicated they would rather use TGC if in-person services require masks and physical distancing and believe HD-TGC should continue to be offered as an option. In interviews, examples of positive reflections discussed include increased convenience for patients and support companions. Some challenges discussed include impaired therapeutic connection and distracted patients.

Conclusions: The COVID-19 pandemic provided an unexpected opportunity to explore the utility of HD-TGC as an option. The majority of GCs indicated their comfort in providing HD-TGC grew over time, and they believed HD-TGC would continue to be provided post-COVID-19.

Safety and Feasibility of Research Lumbar Puncture in Huntington’s Disease: The HDClarity Cohort and Bioresource

Filipe B. Rodrigues¹, Gail Owen¹, Swati Sathe², Elena Pak², Dipinder Kaur², Anka G. Ehrhardt², Sherry Lifer², Jenny Townhill³, Katarzyna Schubert¹, Blair R. Leavitt⁴, Mark Guttman⁵, Jee Bang⁶, Jan Lewerenz², Jamie Levey²,³ (for the HDClarity Investigators), Cristina Sampao², and Edward J. Wild*¹

¹University College London, Huntington’s Disease Centre, UCL Queen Square Institute of Neurology, London, UK
²CHDI Management/CHDI Foundation, Princeton, NJ, USA
³Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
⁴Division of Neurology, Department of Medicine, University of Toronto, Toronto, ON, Canada
⁵Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
⁶Division of Neurology, Department of Medicine, University Hospital of Ulm, Ulm, Germany
⁷Department of Neurology, University of British Columbia, Vancouver, BC, Canada
⁸Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
⁹Department of Neurology, Ulm University, Ulm, Germany
Setting Up a New Multidisciplinary Clinic for Huntington’s Disease
Nicholas Cothros1 and Elvina May-Yin Chu*2
1Division of Neurology, Department of Medicine, Queen’s University, Ontario, Canada
2Department of Psychiatry, Queen’s University, Ontario, Canada

Background: Huntington’s disease (HD) is a rare disease so patient needs may not be well understood by others. Steps taken to setting up a new HD service are described.

Objectives: Understand processes involved in setting up a specialist multidisciplinary HD clinic.

Methods: Multidisciplinary clinical care has been demonstrated to be of value in HD, but clinics vary considerably in the way they have been set up. The authors report observed key components of various HD clinics across the UK and Canada.

Results: Clinics were composed of physicians, allied health professionals, and trainees working in parallel sessions with joint post-clinic debriefing. Efficient administration kept research and clinical streams running seamlessly and minimized wasted appointments. Clinical care often overlapped with research to save patients from repeated travel, which also improved recruitment/retention rates and allowed access to novel treatments in clinical trials.

Conclusions: Securing support from appropriate medical and clinical directors is essential early on. In an academic hospital setting, such combined research and training opportunities are invaluable. Assistance from patient support groups can help to gauge interest in services and patient preferences. Such objective evidence can then be presented when approaching other parties who may have limited knowledge of HD. We argue that success in developing specialized multidisciplinary HD care requires not only an assembly of relevant healthcare professionals but also recruitment of top administrators across multiple academic departments related to healthcare and rehabilitation, in addition to a clearly articulated plan for allocation of clinic space, research facilities, and staff resources.
**Enroll-HD Study Status**

Selene Capodarpa*1 (on behalf of the Enroll-HD Platform Team)

1EHDN, Ulm, Germany

**Background:** Enroll-HD is a clinical research platform that includes at its core an observational, prospective study of HD. The objectives of Enroll-HD are to: (1) enhance the design and expedite the conduct of clinical trials; (2) improve the understanding of the phenotypic spectrum and disease mechanisms; and 3) foster good clinical care.

25,927 participants (19,931 currently active) have been recruited from 178 study sites (157 currently active) in 21 countries (as of July 1, 2021). The data collected from these participants is monitored using a rigorous risk-based process. Recoded data and biosamples are made available to researchers. As of June 1, 2021, more than 350 projects were conducted, and more than 70 publications have been published using the Enroll-HD data.

Enroll-HD also serves as a registry that can be used to facilitate recruitment by identifying potentially eligible participants who can be invited by investigators to participate in clinical trials. To improve support for future clinical trials and observational studies, the study has successfully refocused its recruitment strategy to increase participants in the at risk, premanifest, and early-stage HD participant subgroups.

Throughout the COVID-19 pandemic, the study team encouraged the sites to keep the participants engaged in the study and collect some data through phone contacts. Since the end of Q2 2020, a gradual reopening of the sites has been observed (as of July 1, 2021, 141 sites out of 157 have resumed study activities).

Platform studies are clinical studies that utilize at least one or more types of Enroll-HD platform support. These include site feasibility, study guidance documents and templates, potentially eligible participant listings, study set-up support, monitoring, and data management. The Enroll-HD Clinical Training Portal is an online resource launched in January 2017, where HD research personnel can complete and maintain study-relevant training, presently UHDRS Motor Certification, GCP (all users), and Enroll-HD Plasma Collection (Enroll-HD study users only). With more than 1,850 active users, the portal aims to enable faster, more cost-effective start-up of clinical trials and studies, standardizes the quality of training, and reduces workload at sites.

**Motor Speech Across the Disease Spectrum from Presymptomatic to Mid-Stage Huntington’s Disease**

Jess Chan1, Julie Stout2, Yenni Lie3, Adam P. Vogel*1,4

1The University of Melbourne, Melbourne, Australia
2Monash University, Melbourne, Australia
3Calvary Healthcare, Melbourne, Australia
4Redenlab, Inc., Melbourne, Australia

**Background:** Clinical markers that show change in performance in people with Huntington’s disease during the presymptomatic and prodromal stages remain a target of investigation in clinical medicine. It is likely that future therapies will target individuals in this disease stage, before the underlying pathology takes hold. Alongside genetic and neuroimaging initiatives, behavioral testing has shown promise as a measure of subtle clinical changes in the premanifest phase. Digital speech analytics is potentially a responsive but under-explored feature of premanifest HD (PreHD).

**Objectives:** To investigate the sensitivity of digital speech measures for detecting subtle cognitive-linguistic and fine-motor features presenting in people carrying the expanded HD gene, with and without symptoms.

**Methods:** Speech data were acquired from 110 individuals (55 people with the expanded HD gene, including 14 presymptomatic, PresymHD; 18 prodromal, ProdromHD; 14 early stage HD; 9 mid stage HD; and 55 age- and sex-matched healthy controls). Objective digital speech measures were derived from speech tasks that fit along a continuum of motor and cognitive performance. Tasks included sustained vowels, syllable repetition, and automatic and connected speech tasks. Features quantified speaker articulatory agility, voice quality, and speech-timing. Subjects also completed the Cogstate’s Brief Cognitive Battery and the Purdue Pegboard Test for testing upper-limb fine-motor performance.

**Results:** PresymHD (furthest from disease onset) and healthy controls differed on speech tasks bearing the largest cognitive load for the speaker,
the monologue task. Speech in ProdromHD (within 15 years to estimated disease onset) is characterized by reduced articulatory agility in syllable repetition tasks, as well as altered speech timing, including reduced speech rate and longer and variable pauses. Performance on speech agility tasks correlated with poorer performance on the manual fine-motor test.

**Conclusions:** Only speech tasks with a mix of cognitive and motor demands were able to separate Pre-symp individuals and matched controls. Motor speech tasks alone did not differentiate groups until individuals became closer to disease onset or symptomatic. These data show how ubiquitous behaviors like speech, when analyzed objectively, can provide insight into disease related decline.