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Abstracts

1

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

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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.

2

Disease Burden of Huntington's Disease in a Canadian Setting Using Administrative Health Data

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Background: There is limited evidence of the epidemiological and economic burden of illness for Huntington's disease (HD) in Canada.
Objectives: To characterize the epidemiology, healthcare resource utilization (HRU), and direct healthcare costs for HD using a retrospective study of administrative health data in Alberta, Canada.
Methods: Data from April 1, 2010-March 31, 2020, were extracted for patients ≥21 years of age who were identified with HD using a published algorithm (≥2 HD diagnosis codes within two years). The five-year (2014/15-2018/19) average annual incidence and period prevalence were calculated. Patients with ≥1 year of follow up were included in a burden of illness (BOI) cohort, among whom comorbidities, HRU, and associated costs (inflated to 2020 Canadian dollars) per person-year were examined.

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

Fully Automatic Estimation of Caudate Volume and Volume Change: A Comparison of Atlas and Deep-Learning-Based Approaches

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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-accumbens 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

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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,

Academic Search Ultimate, and Cochrane Library up to March 1, 2020.
Results: From an initial return of 1,579 citations, a total of nine papers were considered eligible for review. These included a qualitative investigation, three case studies, two case series, two uncontrolled pretest-posttest designs, and only one randomized control trial (RCT). Despite the wide range of psychological difficulties that can be experienced by people affected by the HD gene expansion, the adopted interventions only accounted for five main psychological outcomes (anxiety, apathy, depression, irritability, and coping). Further discussion and suggestions for future research are provided for each outcome.
Conclusions: The current literature on psychological interventions in people affected by HD is extremely limited, both in terms of methods and addressed clinical outcomes. Consequently, no conclusions can be offered yet as to which psychological therapy may help this population. As more comprehensive research is urgently needed for this group, the ultimate aim of the present review is to act as a call to arms for HD researchers worldwide to help shed light on the most effective way to translate psychological theory into practice for the benefit of people affected by HD.

5

Use of the ICF-Model for Speech Therapy at Home in Late Stages of Huntington's Disease

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Background: Speech therapy interventions are recommended since the early stages of Huntington's disease (HD) for the management of dysarthria, dysphagia, and communication difficulties. Due to the complexity and the progressive nature of the disease, the access to non-pharmacological therapies in the late stages of HD is challenging, and home-based rehabilitation services are encouraged.
Objectives: The purpose of this study is to describe the application of the World Health Organization's International Classification of Functioning, Disability, and Health (ICF) to the assessment of and goal setting for speech-therapy intervention in the late stages of HD.
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

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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

papers reporting their psychometric properties. All assessments were evaluated with the modified Movement Disorder Society Committee on Rating Scales criteria.

Results: A "core set" of PT assessments was established for HD, including the Six Minute Walk Test, the Timed Up and Go Test, the Berg Balance Scale, and the Short Form 36 (SF-36). Next, we developed guideline-based PT evaluation and plan-of-care decision trees to assist in decision-making and implementation of the clinical guidelines, including specific recommendations for interventions. Finally, we proposed strategies to overcome implementation barriers, such as seeking specialized training in HD, engaging caretakers or family members to help the person with HD to exercise, and establishing clinical pathways that support early referrals of persons with HD to PT.

Conclusions: Future work will address knowledge gaps regarding PT assessments for people with HD and develop knowledge translation tools to facilitate implementation of the clinical guidelines to practice.

7

Enroll-HD Platform Support for Industry and Academic Sponsors

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Background: Enroll-HD is a global research platform with the infrastructure to support clinical trials and studies in Huntington's disease (HD). The prospective, observational, longitudinal Enroll-HD study at the core of the platform is active in 21 countries and has recruited 25,927 participants (19,931 currently active), who have completed standardized clinical assessments and biosample collections at annual visits at 178 study sites (157 currently active) (as of July 1, 2021).

The Enroll-HD platform makes resources and support available to the HD research community, including periodic clinical datasets and biosamples; advice on protocol development; protocol review; assistance with study feasibility, site identification and feasibility; participant recruitment; and site staff training and certification through the Enroll-HD clinical training portal.

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

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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

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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

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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.

11

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

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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.

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

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Background: There is a need for validated assessments for patients with later-stage HD. The Later-Stage HD Assessment (LSA) study aims to provide preliminary clinimetric properties for two such measures: the HD Structured Interview of Function (HD-SIF) and the HD Clinical Status Questionnaire (HDCSQ). Both assessments are administered to a Companion Participant either in-person or remotely, and the properties of these tests will be evaluated using the methods of Classical Test Theory (CTT) and Item Response Theory (IRT).
Objectives: To obtain estimates for the clinimetric properties of the HD-SIF and HDCSQ.
Methods: Up to 170 dyads of Manifest HD Gene-Expansion Carrier (mHDGEC) Participants and their Companion Participants are planned to be enrolled in this study from approximately 20 English-speaking study sites. The study includes two sequential parts. In Part 1, we will use the methods of CTT to evaluate the HD-SIF, a structured interview designed to gather information for making ratings on the UHDRSTM '99 functional scales

(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.

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

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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 dataset (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.

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Medicinal Cannabis in Huntington's Disease

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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

gross ataxia and chorea with shift of her center of gravity. She was commenced on medicinal cannabis at a dose of 0.25 ml sublingual CanniMed (THC: CBD 10:10) on June 15, 2019. The dose of medicinal cannabis was gradually increased. Sister 2 is 51 with manifest HD (stage IV) with a CAG repeat length of 46 with significant oromandibular lingual dystonia and chorea with intractable tongue biting such that every time she ate or spoke or opened her mouth, her jaw would shut lacerating her tongue causing frequent bleeding associated with weight loss and inability to eat. Her UHDRS was [72/124]. She was commenced on medicinal cannabis (THC:CBD: 10:10) at a dose of 0.25 ml at night on September 9, 2018. The dose was progressively increased to 0.5 ml in the morning and 0.75 ml at night.
Results: Sister 1's chorea and ataxia improved, which was confirmed by computerized movement analysis showing greater stability of gait and less drift to the center of gravity. She has since remained stable; the chorea has improved, as has her ataxia. Sister 2 had almost complete resolution of her tongue biting with mild improvement in her chorea. The medicinal cannabis also improved her sense of well-being and back pain.
Conclusions: Our experience suggests that there may be a role for medicinal cannabis in palliative care of patients with later-stage HD with complex symptoms not responding to other treatments.

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

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Background: Predicting disease progression is important to the success of clinical trials involving premanifest (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.
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 ($F_{3,99}=6.725$, $p<.001$ AP, $F_{3,99}=4.551$, $P<.005$ ML, $F_{3,99}= 6.131$, $P<.001$ 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 ($F_{3,99}=5.393$ $P< .002$), especially with EC ($F_{3,99}=7.910$ $P< .001$).
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.

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Novel Neuropsychological Tool in Premanifest Huntington's Disease

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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

Demographics and Cognitive Baseline

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

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

Methods: We administered the LASSI-L to 14 pre-symptomatic 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.

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Determining Plasma Neurofilament Light Cut-Off Points for Predicting Years to Manifest Huntington's Disease Onset

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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: 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). Plasma NfL levels were also correlated with predicted years until 50%, 60%, and 70% probability of HD onset (r=-60, p<0.0001). A receiver operating characteristic curve analysis determined that a plasma NfL cutpoint 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.

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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

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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.

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

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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.

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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)

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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 €3,627) 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.

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

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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 encompass 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.

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

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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.

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Huntingtin Maintains Mitochondrial Genome Integrity and Function

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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.

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

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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.

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

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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.

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

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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 Perception 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.

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

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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 Problematic 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 ($p\leq0.05$).

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.

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Disparities in Palliative Care Utilization Among Hospitalized People with Huntington's Disease: A National Cross-Sectional Study

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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.

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

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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 neuropalliative specialists seek to enhance M&P, identifying the factors explaining levels of M&P is essential to optimize interventions.
Objectives: Adjusting for clinical/demographic covariates 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 variance 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/high with one standard deviation below/above). 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, people 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. Depression, advance care planning (ACP), positive affect, 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 interventions should incorporate ACP and find alternative pathways to achieving social satisfaction.

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

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Background: Death anxiety appears as a persistent trait across the lifespan among people with Huntington's disease (HD) and was recently captured as a patient-reported outcome (PRO): "HDQLIFE Concern with Death and Dying (CwDD)." While palliative interventions in oncology have ameliorated death anxiety, there are none within HD. Before adapting neuropallaitive 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 associated 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 accounting 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. Baseline CwDD predicted 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 predictive 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 stigma should be incorporated within neuropalliative interventions for HD.

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

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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.

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

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Background: Advance care planning (ACP) is a reoccurring 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.

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SELECT-HD: An Adaptive Randomized Controlled Phase 1B/2A Trial of WVE-003 in Participants with Early Manifest Huntington's Disease

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Background: Huntington's disease is caused by the expansion of CAG-repeats (≥36 repeats) in at least one copy of the HTT gene that leads to the expression of the mutant HTT (mHTT) protein. The unaffected copy of the HTT gene encodes the wild-type HTT (wtHTT) protein, which supports many processes important for the health and function of the central nervous system (CNS). Wave has developed WVE-003, an investigational stereopure oligonucleotide designed to selectively reduce the expression of mHTT mRNA while preserving wtHTT mRNA by targeting a single nucleotide polymorphism, SNP3. WVE-003 contains Wave's new PN chemistry, which has been shown to improve the pharmacological profile of oligonucleotides in preclinical studies.
Objectives: The primary objective is to assess the safety and tolerability of single- and multiple-ascending doses of WVE-003 administered intrathecally by lumbar puncture. Secondary objectives include studying WVE-003 pharmacokinetics (PK) in plasma and cerebrospinal fluid (CSF).
Methods: We are evaluating WVE-003 in an adaptive, multicenter, randomized, double-blind, placebo-controlled, phase 1b/2a clinical trial called SELECT-HD. We plan to enroll approximately 36 participants who have SNP3 only on the mHTT allele. We will evaluate CSF biomarkers of neurodegeneration, including neurofilament light chain, and CSF biomarkers of pharmacodynamic effect and selectivity, mutant and wild-type HTT proteins, respectively. The trial is designed to be adaptive, so that PK, safety, and tolerability results from each cohort will inform the dose and dosing frequency for subsequent cohorts.
Conclusions: This first-in-human study will provide proof of concept for pharmacodynamic effects, as well as PK, safety, and tolerability of WVE-003 in early manifest Huntington's disease.

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The Exploration of Establishing a Wechat-Based Virtual Huntington's Disease Cohort

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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.

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

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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, post-synaptic 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 post-synaptic functions in an HD cellular model. The neuroprotective effects of pridopidine are exclusively mediated by S1R activation.

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New Findings on the Mechanisms Driving Pridopidine's Biphasic Dose Response

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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 nucleopore 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 1uM). At higher doses (10 and 100uM) pridopidine's neuroprotective effect decreases. Pridopidine causes S1R-BiP dissociation and reduces S1R oligomerization in a biphasic manner (optimal dose 1uM), 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.

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

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Background: Pridopidine is an oral drug candidate in clinical development for Huntington's disease (HD) and ALS. Pridopidine activates the Sigma-1 receptor (S1R), which enhances neuroprotective cellular pathways. In the PRIDE-HD Ph2 trial, pridopidine 45 mg bid maintained functional capacity at 52 weeks in early HD patients (TFC 7-13) (Δ vs. placebo 1.16, p=0.0003). Neurons release neurofilament light (NfL) protein upon neuronal injury. In HD, NfL levels in biofluids increase with disease progression, serving as a biomarker that correlates with longitudinal decline in function, cognition, and brain atrophy. Reductions in NfL associate with clinical effectiveness of treatment (e.g., Multiple Sclerosis). To date, no treatment has shown maintenance or decrease of NfL levels in HD.
Objectives: To evaluate the effect of pridopidine on plasma NfL levels and its association with TFC in PRIDE-HD at 52 weeks.
Methods: NfL levels in plasma from early HD patients were analyzed at baseline and week 52 (by Simoa methodology). The relationship between NfL and TFC was modeled from all available data at baseline and week 52 using a linear mixed model.
Results: Pridopidine treatment demonstrates maintenance in TFC vs. Placebo at 52 weeks (ΔTFC +0.09, n=37 vs. -1.0, n=41, p=0.0006). Placebo shows an annual increase in NfL (ΔNfL +0.05 log2 pg/ml, n=34), similar to the annual increase observed

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.

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

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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.

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

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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

pridopidine reduces the probability of worsening in TFC by 80% in early HD (p=0.002). Exploratory analysis also shows improvements in the combined assessment of total motor score, TFC, and the symbol digit modality test vs. placebo (Δ0.6, p=0.04). Q-Motor, a quantitative motor test, demonstrated improvement in the finger inter-tap interval vs. placebo at weeks 26 and 52 (Δ-0.034 sec, p=0.035 and Δ-0.044, p=0.03, respectively). P-values are nominal. The primary endpoint in PROOF-HD is mean change in TFC from baseline to Week 65. PROOF-HD is actively enrolling at 30 sites in the U.S. and Canada and 30 sites in Europe (Spain, France, Germany, Poland, Italy, Austria, the Czech Republic, the Netherlands, and the UK). As of September 2, 2021, over 530 patients have been screened, and over 370 patients randomized (over 75% of the total). The screen failure rate is low (15%, 82/533).

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

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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 ≥21years 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.
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.

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

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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 received adequate support following the cancellation of the dosing for the clinical

trials; and (3) would they choose to log onto another presentation with more information. The survey was posted two months after the drug dosing was stopped.

Results: Forty-nine people responded. Only 43% of responders felt they had enough information about the trials. Forty-five percent of responders felt they did not receive enough support to cope with the news; 33% of responders felt they might log onto another presentation; and 63% of responders stated that they would log onto another presentation.

Conclusions: The HD scientific community responded quickly to ensure information about the two halted drug trials was available. Multiple HD organizations provided webinars within two weeks post announcement. Nearly half of the people who responded to our survey felt they still needed more information. Moreover, nearly all the responders said that they might or would log onto another presentation to receive more information. It would be beneficial for organizations such as HDYO to continue to provide ongoing education and support to young people and their families about these drug trials.

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

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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.

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

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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.

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

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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 chorea associated with HD.

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.

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Assessing the State of Care for Huntington's Disease (HD) in the United States: Results from a Survey of Practices Treating HD Patients

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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.

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

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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.

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

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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.

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

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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: POC study assessing SOM3355 efficacy and safety in HD patients presenting chorea.
Methods: In this double-blind, randomized, crossover, placebo-controlled study, 32 patients were randomly assigned to receive placebo and SOM3355 at 100 and 200 mg BID in crossover design over four six-week sequences. The primary endpoint was the improvement of at least two points in the total maximal chorea (TMC) score of the Unified Huntington's Disease Rating Scale (UHDRS) in any SOM3355 period compared to placebo period.
Results: Treatment with SOM3355 induced reduction of TMC score ≥2 points compared to placebo in almost 60% of the patients and even greater reduction of 3, 4, 5, and 6 points in 28.6%, 25.0%, 17.9%, and 10.7%, respectively. Mixed-model analysis

comparing the different periods revealed significant improvement in the TMC score with SOM3355 at 200 mg BID compared with placebo (P = 0.0224), as confirmed in ratings of Clinical and Patient Global Impression of Change. Mild elevations in plasma prolactin levels were recorded with SOM3355 (P < 0.005), consistent with the VMAT2 inhibition profile. SOM3355 tolerability was good with only mild AEs related to β blocking effects.

Conclusions: SOM3355 reduces chorea in HD and has a good safety profile. SOM Biotech discovered that SOM3355 (bevantolol) has VMAT2 inhibitor activity and could be repositioned in the treatment of chorea in HD. A proof-of-concept study was conducted to confirm that SOM3355 effectively reduces Huntington's chorea and has a good safety profile.

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

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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.

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A New Deep-Learning Model for Putamen Segmentation

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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

boundaries (influenced by pathology and scanner protocol). This results in high measurement variability that can reduce the sensitivity of the measure both cross-sectionally and longitudinally. The emergence of deep-learning segmentation tools (convolutional neural networks – CNNs) provide a framework for improving the reliability and sensitivity of the measurement, while also reducing overheads associated with full manual segmentations by expert raters.

Objectives: To develop a CNN that accurately segments the putamen in a range of populations, including HD patients and other conditions where putamen pathology is present.

Methods: We develop a deep-learning method, a 3D convolutional neural network (CNN), that segments the left and right putamen. The 255,000 parameters of the model are iteratively updated in a fully supervised manner by providing the model with 192 T1 scans from an HD population. Each scan has been pre-processed by first brain extracting, bias field correcting, and rigidly registering to a common template space. The CNN method was then applied to HD (different than the training cohort), Alzheimer's disease and multiple systems atrophy populations, and normal controls (18-85 years old). The model accuracy was evaluated qualitatively using visual quality control (QC) and statistically against ground truth labels. Ground truth labels were generated by manually editing labels generated from an atlas-based approach. The CNN was further compared in all tests against an established atlas-based approach, specifically optimized for the putamen (LEAP), which has been shown to outperform other established techniques like FreeSurfer for striatal segmentations.

Results: Three of 80 CNN segmentations failed visual QC inspection across all six validation data sets, compared with 53/80 LEAP segmentations. The mean (SD) dice overlap score for the CNN was 0.9001 (0.0348) vs. 0.85 (0.0362) for LEAP. Compared to the ground truth the CNN overestimates the putamen volume by mean (SD) = 2.5% (9.52%), whereas LEAP overestimates by 14.0% (8.92%).

Conclusions: Our model provides highly accurate, fully automated segmentations of the putamen, with a very high degree of confidence and generalizable across different populations and studies without loss of accuracy.

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Racial Differences in Indices of Disease Burden and Progression in Huntington's Disease

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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.

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

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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.
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 (clinical trials.gov NCT04514367).

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

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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.

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

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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 the 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.

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

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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.

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Treatment and Prescription Patterns in Patients with Huntington Disease: Results from a Real-World Claims Analysis

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Background: Treatment for chorea associated with Huntington disease (HD) typically includes an FDA-approved vesicular monoamine transporter type 2 (VMAT2) inhibitor and/or antipsychotics (APs), per treatment guidelines.

Objectives: This study sought to examine patient characteristics and treatment patterns in three medication cohorts.

Methods: The PearlDiver research database (~53 million patients) was used to identify patients who had ≥2 HD claims (ICD-9-CM 333.4, ICD-10 G10) and ≥12 months of continuous coverage with a medication claim (VMAT2 inhibitor [deutetrabenazine, tetrabenazine] or AP that occurred after HD diagnosis. Three treatment cohorts were generated: VMAT2 inhibitor only, AP only, and combination (VMAT2 and AP). Chi-squared and Student T-tests were used to compare treatment patterns by specialty (neurology versus psychiatry).

Results: 5,838 patients were included for the cohort-based analyses (VMAT2=849, AP=3,725, combination=1,264). Mean/median age (years) and the percent of female patients by cohort were as follows: age (VMAT2=57/59, AP=53/54, combination=53/54); female (VMAT2=60%, AP=57%, combination=59%). Prescription by a neurologist was most common in the VMAT2 cohort, while psychiatrist prescriptions were most common in the AP cohort: neurologist prescription (VMAT2=81%, AP=50%, combination=60%; p<.001); psychiatrist prescription (VMAT2=2%, AP=32%, combination=27%; p<.001). The percentage of patients with a neurology or psychiatry specialty outpatient claim varied among cohorts: neurology claim (VMAT2=47%, AP=49%, combination=59%; p<.001); psychiatry claim (VMAT2=10%, AP=24%, combination=22%; p<.001).

Conclusions: Differences in prescriber specialty and visit frequency varied between cohorts, suggesting that pharmacotherapy regimens may be impacted by provider specialty.

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

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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.

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

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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 morphometry.
Results: Age-related changes in cortical morphometry 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.

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Huntington Disease: Proposal for Care Recommendations in the Premanifest Years

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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.

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

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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.

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"COVID-19 Impact on Genetic Counseling for Huntington's Disease via Telehealth"

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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

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.

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

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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: HDClarity (NCT02855476) is an ongoing international biofluid collection initiative built on the Enroll-HD platform, where clinical assessments are recorded. It aims to recruit 1,200 participants. Biosamples are collected following an overnight fast: blood via venipuncture and CSF via LP. Participants are healthy controls and HD gene-expansion carriers across the disease spectrum. We report on monitored data from February 2016 to September 2019.

Results: Of 448 participants screened, 398 underwent at least one sampling visit, of which 98.24% were successful (ie CSF was collected), amounting to 10,610 mL of CSF and 8,200 mL of plasma. In the total 572 sampling visits, adverse events were reported in 24.13%, and headaches of any kind, and post-LP headaches in 14.86% and 12.24%, respectively. Frequencies were less in manifest HD; gender, age, body mass index, and disease burden score were not associated with occurrence of the events in gene-expansion carriers. Headaches and back pain were the most frequent adverse events.

Conclusions: HDClarity is the largest CSF collection initiative to support scientific research into HD and is now established as a leading resource for HD research. Our data confirm that research LP in HD are feasible and acceptable to the community and have a manageable safety profile.

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Patient and Caregiver Perspectives on Use of Telehealth During the COVID-19 Pandemic from a Multidisciplinary Huntington's Disease Clinic

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Background: The coronavirus pandemic saw technology evolve as outpatient clinics faced restriction of in-person visits as part of infection control. Reliance on telemedicine using two-way audio-video communication significantly increased. It was observed to be convenient and cost-effective, reduced no-show rates, and fostered sustained engagement. Enhanced flexibility from short notice scheduling benefitted patients. Greater time value was perceived by patients and reduced reliance on caregivers. Disadvantages included barriers of access to internet connectivity or equipment.
Objectives: We aimed to retrospectively survey patients with Huntington's disease (HD) seen via telehealth for clinic visits. We evaluated usability, learnability, interface quality, reliability, and future use.
Methods: This qualitative survey used the 21-item Telehealth Usability Questionnaire. Close-ended responses ranged from strongly disagree to strongly agree scored on Likert scale (1 through 7). Averages were calculated to examine attitudes towards telemedicine. Spearman correlation test was performed to detect attitude biases between patients and caregivers.
Results: Respondents were more likely than not to strongly agree with survey statements. There was no bias between patient and caregiver attitudes. Average attitude scores 3.57 to 7.00 suggested favorability and improved convenience when telehealth was used in complement to in-person visits, without detriment to patient-provider communication.
Conclusions: This study demonstrated telehealth is favored by caregivers and patients with HD. This population with specific physical, cognitive, and psychiatric needs can benefit from adaptive systems that enhance compliance.

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Setting Up a New Multidisciplinary Clinic for Huntington's Disease

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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.

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Enroll-HD Study Status

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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.

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

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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 Presymp 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.