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Abstracts

1

FEEDhd: Facilitating Effective Eating with Doddlebags

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Background: Eating behaviours in Huntington's Disease (HD) are a subject that has been relatively unexplored in contemporary research. It is common for people with manifest Huntington's Disease to experience significant weight loss, but the mechanism by which this occurs appears to be little understood and contested by multiple plausible explanations. This research will assess the efficacy of a proposed solution to the practical barriers that HD creates; the reduced ability of a person with manifest HD to feed oneself easily, safely, and effectively.
Methods: This study will provide participants with a selection of Doddlebags products, instruct them on how to use them, and encourage them to incorporate the products into their mealtimes wherever possible. The ease-of-use and suitability of the Doddlebags will be assessed through a food diary and semi structured interview, while the psychosocial impact on the participant will be measured using two self-report measures—the Adult Eating Behaviours Questionnaire (AEBQ) and the Burckhardt Quality of Life Scale (QoLS).
Hypothesised Findings: The hope of the researchers is that the Doddlebags will not only lead to increased perceptions of independence among participants, making it easier for people with HD to independently self-feed, or be fed by a carer more easily, but also that they will provide a statistically significant uplift in either/both scores on psychometric tests, indicating improved mood and wellbeing, or BMI, with a trend towards the healthy BMI range. This would suggest that the Doddlebags are an efficacious method of feeding in HD.
Impact on Clinical Practice (for Our Patients and Our Staff): Evidence suggests that the current common solution for weight loss in HD—high calorie supplements—are generally disliked and not well tolerated, with the majority of prescriptions discarded rather than being consumed. Therefore, the use of Doddlebags represents a solution that allows patients to continue eating normal food on their own terms, with minimal wastage and much reduced cost to the National Health Service.

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BMI as a Correlate of Disease Progression in Huntington's Disease

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Background: Huntington's Disease (HD) is an inherited neurological disease that affects around 12 people per 100,000 in the United Kingdom. Huntington's Disease is typically characterised by uncontrollable, hyperkinetic movements known as Chorea, as well as cognitive and psychiatric issues. One symptom that is often unmentioned during the disease pathway of a person with HD is that of unexplained weight loss. Weight loss is a common feature of manifest HD and appears to have multiple interactions with other symptoms seen in HD, heavier weight has also been associated with slower generalised progression of the disease.
Objective: This research builds upon previous work by the authors that focused on motor symptoms only and expands the focus to encompass cognitive and psychological components of the illness. As with the previous research, this project continues to be an analysis of the Enroll-HD study data set, a multinational, longitudinal, observational study of ~25,000 people with Huntington's Disease.
Methods: The data were imported into RStudio, where the researcher performed a range of statistical analyses, including linear and smoothed regressions, as well as boxplots and multiple linear regression analysis.

Results: The trend towards a statistically significant relationship between BMI and motor as patients enter the "underweight" range is mirrored within other aspects of the disease. This suggests that underweight patients are more likely to have advanced symptoms of HD than people of a normal weight. Therefore, the noncausal relationship between BMI and HD symptomatology is much more holistic than previously thought and being underweight impacts multiple aspects of a person's Huntington's than merely their motor abilities.
Impact on Clinical Practice (for our patients and our staff): This is further evidence that a more proactive approach to the presence of weight loss in people with HD is essential, as being underweight may be accelerating many aspects of disease progression. More efforts should be made to routinely monitor the weight of people with HD to arrest declines in weight before patients become underweight as the association with a worsening disease pathway becomes clearer.

3

Unraveling the Sequential Pattern of Memory Deficits along the Huntington Disease Continuum: Insights from the LASSI-L

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Background: Huntington's disease (HD) is characterized by early-onset cognitive decline, with impairments in psychomotor speed, executive functioning, and memory. The Loewenstein-Acevedo Scale for Semantic Interference and Learning (LASSI-L) has detected these deficits from the earliest stages of HD by a distinctive combination of controlled learning, timed recall, and semantic interference. As HD advances, participants encounter growing difficulties across sections of the LASSI-L.
Objective: The LASSI-L was employed to methodically track the progression of cognitive deficits in HD. To determine a pattern in which test sections began posing challenges for patients, our objective was twofold: to establish an efficient method for staging cognitive changes using a single test, and to elucidate how disease progression serially impacts facets of memory.
Method: We administered the LASSI-L to 132 participants (89 HD and 43 matched controls). HD participants were classified into four subgroups—Far, Mid, Near, and Manifest—based on their CAG-Age-Product scaled (CAPs) scores. We employed ANOVA and Tukey's pairwise comparison to analyze demographics and performance across LASSI-L subsections.
Results: Our study unveiled a discernible pattern of escalating memory-related deficits in HD, beginning with proactive semantic interference (PSI), progressing to retroactive semantic interference, and culminating in the inability to recover from PSI. Remarkably, 98% of HD participants exhibited initial deficits on PSI, and 84% followed the complete trajectory.
Conclusions: LASSI-L is sensitive at distinguishing cognitive stages of HD. It serves as a unique tool for step-by-step accumulation of deficits, providing critical insights into the patterns of disease progression and cognitive decline in HD.

4

Stroop Color Word Test: A Directional Administration Comparison in Huntington's Disease

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Background: Huntington's disease (HD) is a neurodegenerative disorder characterized by motor, cognitive, and behavioral abnormalities. The Stroop Color Word Test (SCWT) has been instrumental in detecting and tracking cognitive impairments in HD, particularly through its Word-Reading subtask, which critically evaluates executive-function and

processing-speed. The SCWT can be administered with instructions to read either horizontally or vertically. Although both versions have been used in HD-specific research, it is not clear whether reading direction affects test sensitivity or subject performance.
Objective: To investigate the effect of horizontal versus vertical reading instructions on SCWT task performance in HD.
Method: We administered both the Golden (vertical) and Enroll-HD (horizontal) versions of the SCWT to 46 HD participants at Beth Israel Deaconess Medical Center and Vanderbilt University Medical Center in a randomized counterbalanced order. Paired t-test analyses compared performances for both raw and norm-adjusted scores.
Results: Mean age was 47.26 (SD=16.11), ISCED education score was 3.80 (SD=1.07), CAG repeat length was 43.78 (SD=3.09), and Total Motor Score was 21.29 (SD=16.39). A significant performance discrepancy was observed for Word-Reading ($p = 0.035$) and Color-Naming ($p = 0.027$) subtasks based on orientation, which remained significant for Word-Reading ($p = 0.030$) after normed correction. No significant difference was detected for Color-Word Interference in either raw or normed score comparison.
Conclusions: Findings suggest that vertical administration of SCWT may be more sensitive to HD-related neuropathological changes. This novel insight into HD performance could have implications for future research in diagnostic and clinical trial applications for HD.

5

Investigating the Influence of Semantic Interference on Clustering Strategies in Premanifest Huntington's Disease

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Background: Huntington's disease (HD) typically manifests as a triad of motor disturbances, behavioral anomalies, and an early cognitive decline featuring memory, learning, and executive function impairment. The Loewenstein-Acevedo Scale for Semantic Interference and Learning (LASSI-L), a verbal learning test, encourages explicit semantic clustering strategies during initial encoding (list A) and then promotes inference when switching to a semantically-related list B. Premanifest HD (Pre-HD) patients have shown a significant susceptibility to this interference. However, it remains uncertain whether this sensitivity is due to diminished efficacy of their clustering strategies.
Objective: To understand the impact of semantic interference on semantic clustering strategies on the LASSI-L among preHD patients.
Method: The LASSI-L was administered to 30 participants with HD and 23 Healthy Controls at Beth Israel Deaconess Medical Center. A chance-adjusted semantic clustering ratio score was calculated from free recall sections and compared between groups using independent T tests.
Results: A significant difference was observed for clustering scores on List B Free Recall ($p=.0003$), but not on List A Free Recall ($p=0.445$) or List A Free Recall after a short delay ($p=0.118$). Interestingly, List B recall did not improve with semantic cueing.
Conclusions: In preHD patients, semantic interference appears to significantly undermine clustering strategies, leading to diminished encoding and a temporary drop in performance when first attempting to learn a new list. Future versions of the LASSI-L incorporating recognition tasks could offer deeper insights into the origins of these disruptions.

6

Racial and Ethnic Differences in Suicidal Ideation in North American Patients with Huntington's Disease: Analysis Using the Enroll-HD Data Set

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Background: Suicidal ideation (SI) and suicidality are leading causes of morbidity and mortality among Huntington's Disease patients. However, racial and ethnic differences in SI have not been reported.
Objective: To identify racial and ethnic differences in a history of suicidal ideation among HD patients using the ENROLL-HD, 2020 periodic dataset.
Methods: In this cross-sectional study, we evaluated the odds of reporting a history of suicidal ideation (yes/no) across different racial and ethnic groups

during the baseline ENROLL-HD visit. We used multivariate logistic regression models adjusting for sex, age, Total Functional Capacity score (TFC), history of cognitive impairment, employment status, educational attainment, and participant's residential location.

Results: There were 4,717 genetically confirmed HD participants (36+ CAG repeats) in North America. 56% of participants were female, and 10% (n=494) identified as a race or ethnicity other than White. 3.4% identified as Latino, 2.3% as Black, 1.1% as Native American, and 0.7% as Asian. Female participants had higher odds of a history of SI (OR 1.15, CI 1.00–1.30). Native American participants had higher odds of a history of SI when compared to White participants (OR 2.36, CI 1.37-4.06). This difference persisted when adjusting for biological and sociodemographic (AOR 2.27, CI 1.3- 3.96, and AOR 2.17, CI 1.22–3.84).

Conclusions: Native American participants with HD have higher odds of experiencing SI than other groups. Qualitative studies with Native American patients with HD are needed to better understand specific risk factors of SI in this patient population and identify culturally appropriate interventions.

7

Real World Experience with Deutetrabenazine for Huntington's Disease Chorea

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Background: Huntington's disease (HD) is a hereditary neurodegenerative disorder with a hallmark feature of chorea. While no disease-modifying therapies currently exist for HD, symptomatic treatment of HD chorea includes FDA-approved VMAT2 inhibitors tetrabenazine (TBZ) and deutetrabenazine (DTBZ). DTBZ was more recently approved, (2017) and while structurally similar to TBZ, DTBZ has a unique pharmacokinetic profile that allows for a longer half-life, reduced plasma fluctuations, and less frequent dosing. In pivotal trials, DTBZ seemed to have an improved safety and tolerability profile over TBZ, but real-world data to confirm this are lacking.

Objective: Here, we evaluate our real-world clinical experience with DTBZ for HD-associated chorea.

Methods: We performed a retrospective chart review of all HD patients who initiated treatment with DTBZ from 01/17 to 05/19 at the University of Alabama at Birmingham. Total Maximal Chorea (TMC) scores, patient-reported subjective efficacy, dosing information, and subjective reports of adverse events were abstracted for each patient.

Results: Our review included 58 patients with a mean length of treatment of 476.4 days. In the reviewed time period, the mean treatment difference in TMC was 4.4. The combined total rate of occurrence of any adverse events was relatively low at 32.8%, and the most commonly reported adverse events were sedation (15.5%), insomnia (6.9%), and diarrhea (3.4%).

Conclusions: Our real-world data supports current literature indicating that DTBZ is an effective and well tolerated treatment for HD-associated chorea. Further studies repeating this on a larger scale, across a greater geography and practice pattern, are needed.

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Prenatal Effects of Mutant Huntingtin

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Background: Huntingtin (*HTT*) is expressed in foetal brain and foetus-derived placenta tissues which contribute to neurodevelopmental programming of offspring. *HTT* knockout models show embryonic lethality, demonstrating its developmental importance and potential to impact later-life outcomes. Despite this, *HTT*'s prenatal role remains poorly understood, and the contribution of mutant *HTT* (*mHTT*) to *placental* dysfunction has never been explored.

Objectives: 1) Provide insight into *mHTT*-driven changes within prenatal tissues through immunohistological, transcriptomic and proteomic comparisons of foetal brain and placenta. 2) Explore differential impacts on males and females. 3) Determine temporospatial *HTT* expression within the placenta.
Methods: This study explores the effect of *mHTT* on placental and foetal development in knockin Hdh^{Q50} (Q50) mice, a model with an *HTT* mutation within typical adult-onset HD range. Placenta and brains at embryonic day (E)14.5, E16.5 and E18.5 from four groups (male and female WT and Q50, *N*=16) will be analyzed for cell counts, volume, HTT expression, and microglial number (brain), as well as endocrine and glycogen cell number (placenta). RNAseq and proteomic analyses (N=6) will assess *mHTT*-driven gene expression changes and protein abundance effects within these tissues.

Data collection is currently ongoing, data is expected to be presented at the Huntington Study Group® conference.
Relevance: Early-life detection of HD pathology presents novel intervention targets with potential to delay or reduce later-life deterioration. This study is the first to investigate the impact of *mHTT* on placental function and its consequences for embryonic neurodevelopment, thus marking the earliest known manifestation of HD signs.

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Revisiting Stem Cell Therapy for Huntington's Disease: Analysis of Cell Surface Markers along with Donor Age and Passage Number of Bone Marrow–Derived Mesenchymal Stem Cells on Treating Motor Deficits in R6/2 Mouse Model of Huntington's Disease

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Background: Huntington's disease (HD) is a fatal neurodegenerative disorder caused by CAG repeat expansions in the Huntingtin gene (*HTT*). There is no cure. Previous reports show the therapeutic effects of mesenchymal stem cells (MSCs) in rodent models of HD. However, the therapeutic effect of MSCs for HD depends on the passage number of MSCs. Higher passage (P40 to P50) delayed the onset of HD symptoms, most likely through the release of neurotrophic factors.
Objective: The present study examined the two critical aspects – the donor age and the passage number of the bone marrow derived MSCs (BM-MSCs) in the context of alleviating motor deficits in R6/2 mice.
Methods: BM-MSCs obtained from 5-week-, 6-month-, and 10-month-old mice at different passage numbers were intrastriatally transplanted into the R6/2 HD mice. Animals underwent a battery of behavior tests to assess HD symptoms following treatment. Further, the BM-MSCs were sorted using FACS for various surface-markers to identify a subpopulation of MSCs having the maximum therapeutic effects.
Results: Our findings indicate that higher passaged MSCs, derived from a young donor, alleviates motor deficits in R6/2 mice. Further, BM-MSCs that are $CD90^+$ alone and $CD105^+$ alone show reduced survival and increased morphological changes over time in culture when compared to the BM-MSCs containing mixed populations. Moreover, the Sca1+ cells were found to be a dominating subpopulation of MSCs at all passages.
Conclusions: Identifying a specific subpopulation of MSCs with specific cell surface markers is an important factor when designing MSCs-based therapies for HD.

Support for this study was provided by the Neuroscience program, the College of Medicine, the E. Malcolm Field and Gary Leo Dunbar Endowed Chair of Neuroscience and the John G. Kulhavi Professorship in Neuroscience at CMU

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Trunk Instability During Single Task, Dual Task, and Fast Paced Gait in Huntington's Disease

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Background: Trunk instability during gait remains understudied in Huntington's Disease (HD). Abnormal trunk range of motion (ROM) and variability are two potential measures of postural instability and biomarkers for fall risk in HD.
Objective: To determine trunk ROM alterations during simple and more complex gait tasks in HD.
Methods: Sagittal, coronal, and transverse trunk and lumbar ROM were quantified using an inertial sensor system (APDM™) for 17 participants with HD (56.5 ± 9.3 years) and 17 aged-matched controls (55.0 ± 9.7 years). A 2-minute walk test (2MWT) was used to measure gait variables under single-task (ST), fast-paced (FP), and dual-task (DT) conditions. Mann-Whitney tests or unpaired t-tests were used to compare trunk and lumbar ROM and the ROM coefficient of variation [(CoV) = SD/mean] between HD and control participants.
Results: HD participants had increased trunk ROM in the sagittal plane during ST (p=0.0153), FP (p=0.0153), and DT gait (p=0.0032) compared to controls. The HD group also had a trend of increased lumbar ROM in the sagittal (p=0.056) and transverse planes (p=0.056) under DT conditions, as well as increased lumbar ROM in the sagittal plane during ST gait (p=0.0143). There was a significant increase in trunk and lumbar CoV in all planes in all three conditions in HD (p<0.0001 – p=0.0453).
Conclusions: Worse trunk stability, indicated by increased trunk and lumbar ROM and CoV during gait, might serve as biomarkers for falls and instability in patients with HD. In future work, such measures can be associated with postural instability and falls.

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A Clinical Study of Huntington's Disease from Northern India

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Background: The mutation of the CAG triplet in the Huntingtin (*HTT*) gene results in a pathological expansion of CAG repeats, leading to Huntington's disease (HD), a rare neurodegenerative disorder. The clinical triad of HD comprises motor impairment, cognitive decline, and psychiatric disturbances. The amount of literature on Indian HD patients is limited.
Objective: To describe the characteristics of persons with living with HD from a tertiary care Indian movement disorder centre.
Methods: A retrospective chart review was done to identify all genetically confirmed cases of HD following up in our centre between 1stJan 2020 and 1stJune 2023. All relevant clinical, radiological, and genetic information were collected and analysed.
Results: We recruited 37(24 males) unrelated persons living with HD for this study. The mean(SD) age of the cohort and the average age at onset of the symptoms were 43.14(14.01) and 36.70(12.66) years, respectively. In 31(83.78%) patients, chorea was the first symptom, and 4 patients reported behavioural symptoms at the onset preceding chorea. Two patients presented with juvenile parkinsonism. All patients had chorea and oculomotor abnormalities; other major manifestations were cognitive impairment (28; 75.68%), psychiatric/behavioural abnormalities (25; 67.57%), ataxia (14; 37.84%), bradykinesia/parkinsonism (12; 32.43%), dystonia (8;21.62%), and hyperreflexia (19;51.35%). Family history was positive in 86.5% patients and paternal transmission was common. The mean (SD) CAG repeats were 47.25(5.47). The common imaging abnormality was bilateral caudate atrophy (67.57%) and diffuse cerebral atrophy (43.24%).
Conclusions: The results from our study suggested that characteristics of the HD cohort from the Northern part of India overlaps with that of from other parts of India.

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Minds & Movement: Evidence-based Guidance for Psychological Interventions for People with Huntington's Disease, Parkinson's Disease, Motor Neurone Disease, and Multiple Sclerosis

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Background: Minds & Movement is a project led by Lancaster University along with the Faculty of the Psychology of Older People and Division of Clinical Psychology of the British Psychological Society to produce the first UK national guidance on psychological approaches for people with motor neurodegenerative disorders.
Objective: The aim of this project is to offer evidence-based recommendations for providing psychological support to individuals living with the following four motor neurodegenerative conditions: Huntington's disease, Parkinson's disease, motor neurone disease, and multiple sclerosis.
Methods: To inform the contents of the guidance, a review of over 10,000 studies was carried out in collaboration with national experts on each of the included neurodegenerative conditions.
Results: For people with Huntington's disease, approaches such as cognitive behavioural therapy (CBT), mindfulness-based interventions, and acceptance and commitment therapy (ACT) should be considered in light of preliminary positive evidence. However, at this stage the literature is too sparse to recommend any specific therapy for Huntington-specific psychological issues. Until further evidence accrues, recommendations may be drawn from the current literature involving other neurodegenerative conditions.
Conclusions: The guidance is now published and available for free for all psychologists and any other health professionals who wish to have easy access to up-to-date evidence-based recommendations on Huntington's disease and other motor neurodegenerative conditions.

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Emotion Recognition Deficits in People with Huntington's Disease: 30 Years in Review

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Background: People with Huntington's disease (HD) may experience a wide range of neuropsychological difficulties. Among these, deficits of emotion recognition have received increasing attention over the last few decades. However, the characterisation of such deficits across different disease stages (e.g., manifest v. premanifest) or different types of stimuli and sensory modalities is currently unclear.
Objective: On the 30th anniversary of the discovery of the *HTT* gene, the aim of the present study was to shed light on the evidence on emotion recognition deficits in HD accrued over the past three decades.
Methods: A systematic review of the literature from January 1993 to March 2023 (PROSPERO registration: CRD42023398649) was carried out across four major databases: MEDLINE, PsycINFO, Academic Search Complete, and CINAHL.
Results: From an initial return of 8,563 citations, 52 studies were considered eligible for inclusion. The majority of these consistently reported significant deficits of emotion recognition in people with manifest HD based on visual tasks involving facial stimuli. Preliminary evidence was also found for deficits based on emotional body language stimuli, as well as auditory, olfactory, and gustatory tasks. The literature involving emotion recognition in people with premanifest HD was instead found to be sparser and still inconclusive.
Conclusions: The evidence from the last 30 years consistently supports the presence of deficits of identification of emotions from facial stimuli in manifest HD. However, further investigations are warranted to clarify whether such impairments also affect other sensory modalities, as well as individuals at the premanifest stage of the condition.

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"I Wouldn't Even Know What to Ask for": Patients' and Caregivers' Experiences of Psychological Support for People with Huntington's Disease in Italy

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Background: People with Huntington's disease (HD) often experience psychological difficulties

linked with disease progression and adjustment to living with a chronic condition, which are also frequently shared by their informal caregivers (e.g., partners). Although limited, the current literature on psychological care for people with HD shows that interventions have the potential to drive improvements in mental health and quality of life. However, the experience of accessing and receiving psychological support for HD remains unclear across several countries.

Objective: This study explored the experiences of psychological support for HD from the perspectives of patients and caregivers living in Italy.

Methods: Qualitative semi-structured interviews were carried out with 14 participants—seven patients with early manifest HD and seven partners acting as their caregivers. The resulting data were analysed through thematic analysis.

Results: Four overarching themes were identified: 1) availability of psychological support in HD, 2) barriers to accessing psychological support, 3) enablers to accessing psychological support, and 4) future development of public psychological provision in HD.

Conclusions: In Italy, patients and caregivers perceive public psychological support for HD as unavailable or inadequate, and private therapy is often seen as unaffordable. Barriers such as distrust in public healthcare and preconceptions about therapy may limit access, while advice from HD organisations and seeking therapy for other reasons may act as enablers. Strong emphasis is put on the need for accessible public psychological support throughout all stages of the condition.

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

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

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

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

EHDN is financially supported by the CHDI foundation.

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Enroll-HD Platform Biosample Resources

Enroll-HD Platform Team

CHDI Foundation, Inc., New York, USA

Summary: Enroll-HD is a clinical research platform that includes at its core a global observational study of Huntington's Disease (HD) families who

are followed annually. As of July 1, 2023, 29,930 participants have been recruited from 186 sites in 23 countries, in Europe, North America, Latin America, and Australasia. 21,348 of those participants are still current (i.e., no mortality/end form). In its capacity of clinical research platform, Enroll-HD provides high-quality coded clinical data and biosamples to qualified researchers in the Huntington's Disease research community via a straightforward request process (https://enroll-hd.org/for-researchers/). Due to its longitudinal nature, more than 78,000 blood kits have been collected in Enroll-HD to date. Currently, 12 different types of biosamples collected in 3 different studies (Enroll-HD, HDCSF/HDClarity, TRACK-HD/TRACK-ON) are available via the Enroll-HD platform, and additional biosample collections are in the planning stage. Nonrenewable biosample resources require review and approval by the Enroll-HD Scientific Review Committee (SRC) before release, whereas renewable resources can be released without SRC review. All biosample distributions come with a material, shipping and handling fee, and a biosamples use agreement must be signed before biosamples can be shipped.

Currently available biosample resources include Lymphoblastoid cell lines (LCLs), DNA from LCLs, DNA from whole blood, Peripheral Blood mononuclear Cells (PBMCs), buffy coat, EDTA plasma, Li-Hep plasma, CSF, cells from CSF, Serum, PAX gene RNA, and buccal swabs.

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Enroll-HD Platform Data Resources

Enroll-HD Platform Team

CHDI Foundation, Inc., New York, USA

Summary: Enroll-HD is a clinical research platform that includes at its core a global observational study of Huntington's Disease (HD) families, followed annually. As of July 1, 2023, 29,930 participants have been recruited from 186 sites in 23 countries (Europe, North America, Latin America, Australasia). 21,348 of those participants are still current (i.e., no mortality/end form). Enroll-HD provides high-quality coded clinical data and biosamples to qualified researchers in the HD research community via a straightforward request process (https://enroll-hd.org/for-researchers/). Every 1–2 years an easy access Enroll-HD data set (periodic dataset, PDS), including approximately 80% of the variables collected, is made available to qualified HD researchers. The last Enroll-HD PDS (PDS6) has been made available in January 2023. The risk for participant identification from the PDS is low, but if researchers request non-PDS variables, the risk for participant identification may be increased. Therefore, a specified dataset (SPS) request must be reviewed and approved by the Enroll-HD Scientific Review Committee (SRC). In addition to Enroll-HD, clinical data can be requested from the studies Registry, HDClarity, and TRACK-HD/ON. A large, easy-access Registry dataset (RDS) prepared in a format similar to the Enroll-HD PDS can augment the Enroll-HD PDS and thereby increase the total number of participants for modeling purposes. The RDS can be requested by contacting the EHDN Scientific Bioethics Advisory Committee (SBAC). Datasets are prepared free of charge. In addition to clinical data, the Enroll-HD platform distributes smaller imaging, brain morphometric/volumetric, genome-wide association studies (GWAS), RNAseq, MiSeq, methylation, and proteomics datasets collected across HD studies.

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Toward Improved Imaging of the Ventricular System in Individuals with Manifest Huntington's Disease

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Background: Cerebral ventricular enlargement (cVE) can be caused by several processes, such as aging, diseases, injury, and pharmacological intervention. Huntington's disease (HD) causes ventricular enlargement with rare occurrences of normal pressure hydrocephalus (NPH). Additionally, drug-induced ventricular changes have been observed in HD clinical trials (e.g., GENERATION HD1 [NCT03761849]) occasionally coinciding with NPH. Commonly used volume-based imaging met-

rics of the ventricular system showed no consistent relationship with changes in clinical data, leaving the potential consequences of drug-induced cVE unclear.

Objective: We characterized a battery of NPH-relevant imaging features with an aim to enable an improved understanding of the NPH risk and the relationship between cVE and clinical status.

Methods: Sixteen NPH-specific neuroradiological risk measures were derived from images of selected patients with HD who participated in tominersen clinical trials (N = 305) in a radiological review of six blinded neuroradiologists. The sample covered placebo and treated cases with/without clinical suspicion of NPH. Performance metrics included intra- and inter-rater reliability; responsiveness; relationships with clinical, demographic, and other imaging measures; and predictive value of NPH.

Results: Excellent to poor reliability, and moderate to low responsiveness were observed, with numerous significant baseline and change associations between the risk measures and clinical, imaging, and demographic scores.

Conclusions: Some NPH-risk measures demonstrated a considerable potential to uncover novel anatomo-clinical correlations and advance understanding of mechanisms behind HD- and treatment-associated cVE. A more thorough, ideally multivariate assessment will be required in the future to quantify the clinical validity and potential to predict the risk of NPH.

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A Neurofilament Light Chain Protein Case Story—Test-Retest Reliabilities Observed in GENERATION HD1, a Study of Tominersen in Adults with Manifest Huntington's Disease

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Background: Neurofilament Light Chain (NfL) is a key biomarker in Huntington's disease. To use NfL in clinical trial settings it is critical the methodology is reliable and reproducible.

Objective: To repeatedly test the same samples using the same methodology to directly assess NfL SIMOA reliability and reproducibility.

Methods: Two laboratories simultaneously analysed CSF NfL with the Quanterix SIMOA and NfL kit. Pearson's and Spearman's rank correlation tests and Intraclass correlation Coefficient (ICCs) were used to determine assay reliability.

Key trial data generated with regulated laboratory practices (Lab A, n=2,052 samples, four selected visits) were supplemented with higher-resolution research use-only data (Lab B, n=5,121 samples, all available visits).

Results: Inter and intra-laboratory comparisons of NfL data generated from identical samples indicated poor reliability and replicability (ICC1 < 0.5). Poor reliability may have been due to several factors, including kit-related issues. Limited reliability of NfL data can severely affect the sensitivity to detect associations with other endpoints. Simple main effects, such as dose arm-dependent average change from baseline, may be less affected. To overcome the issues identified here, the tominersen Phase II trial GENERATION HD2 (NCT05686551) will employ a new NfL clinical trial assay with improved characteristics.

Conclusions: To maximise the use of NfL as a biomarker in HD, it is critical to improve the reliability of assay platforms and to minimise inter- and intra-laboratory variation. Here the NfL SIMOA assay showed limited performance under real-world clinical trial conditions and may require additional improvement and extensive planning for clinical utility.

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Enroll-HD Platform Support for Industry and Academic Sponsors

Enroll-HD Platform Team

CHDI Foundation Inc, New York, USA

Summary: Enroll-HD is a global research platform with 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 recruiting at 157 clinical sites

in 23 countries. Since the study began in 2012, 29,930 participants have been enrolled and have completed standardised clinical assessments and biosample collections at annual visits (figures as at 1-Jul-23).

Enroll-HD makes multiple resources available to the HD research community. These include clinical datasets and biosamples, scientific and clinical advice on protocol design, study feasibility, site identification, support with site feasibility and participant recruitment, and site staff training and certification via a dedicated clinical training portal.

Long-standing relationships with clinical sites have been established through operational management and monitoring of Enroll-HD and platform studies; this enables well-informed site identification and feasibility assessment based on extensive knowledge of sites' capabilities and historic study performance. This site intelligence is further supported by Enroll-HD study data, which enables powerful in-silico screening using study-specific inclusion criteria to identify potentially eligible participants; the Enroll-HD HD Clinical Trial Site Certification scheme, which evaluates capability for HD clinical trial participation against a set of standard minimum criteria; and the HD Global Site Investigator (GSID-HD) feasibility database.

The European Medicines Agency has issued a qualification opinion for Enroll-HD as a data source and infrastructure for post-authorisation monitoring of medicinal products for HD.

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The European Huntington's Disease Network (ehdn.org): Structure and Function

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

EHDN hosts a bi-annual meeting, one of the world's largest conferences dedicated to HD.

EHDN Working Groups, Task Forces, and the Think Tank address key research topics, and EHDN further supports researchers by awarding seed funds, supporting consortia bids, and identifying funding opportunities. EHDN partners with the Movement Disorders Society on a series of HD online education courses and a fellowship exchange programme which facilitates training of young professionals from countries where HD care and facilities are developing.

EHDN offers review of clinical trial and study protocols, providing an independent expert opinion, with endorsement given for protocols of high scientific and ethical quality.

EHDN is governed by an Executive Committee, overseeing activities and scientific strategy, and a Scientific Bioethical Advisory Committee who advise on research proposals and clinical trial protocols.

EHDN Central Coordination manages operations, with regional staff linking the EHDN and clinical centres, liaising with the HD patient and research community, and monitoring Enroll-HD study and platform study data.

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

EHDN is financially supported by the CHDI Foundation.

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The Huntington's Disease-Behavioral Questionnaire (HD-BQ): An Examination of Problematic Behaviors in Huntington's Disease

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Background: The HD-BQ, a new 30-item measure with excellent validity and reliability for assessing behavior in Huntington's disease (HD), requires no training to administer and has both self-report and caregiver versions.
Objective: Examine the utility of the HD-BQ for identifying behavioral issues in a large well-characterized cohort of mild-moderate individuals with HD followed at one academic research center.
Methods: The HD-BQ was administered to 99 healthy controls (HC) and 81 manifest HD individuals and their caregivers. Independent-student-t tests compared total scores between HC vs. HD and caregivers vs. HD. Chi-square analyses compared proportions of item responses for each group.
Results: Mean total HD-BQ score for HC was 12 while that for HD subjects was 31, indicating greater behavioral issues ($t = 7.77$, $p < 0.001$). Caregivers rated HD individuals 11 points higher than HD individuals rated themselves ($t = 3.34$, $p < 0.001$), suggesting that HD individuals were actually worse than their self-report ratings. Mild HD (Total Functional Capacity [TFC] ≥ 11) endorsed few behavioral issues compared to moderate HD (TFC ≤ 10) individuals. Behaviors endorsed by HD individuals reflected executive dysfunction, anxiety, and restlessness/fidgetiness. Caregivers endorsed additional behavioral issues such as impulsivity, memory problems, agitation, and poor judgment for their HD counterpart—a discrepancy that widened with disease progression.
Conclusions: We conclude that the HD-BQ identified a broad range of behavioral issues in HD. Maybe not surprisingly, caregivers reported even greater rates of behavioral problems, perhaps, in part, related to HD patients' well-described anosognosia for personal deficits, which has significant implications for the use of self-report measures in HD research.

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Development of an NfL Clinical Trial Assay to Support GENERATION HD2, a Phase II Trial of Tominersen

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Background: There is increasing interest in understanding the clinical utility of Neurofilament Light (NfL) as a biomarker for disease activity in individuals with Huntington's disease. While there are several research-use NfL assays in existence, measurement of NfL in clinical trial settings requires a robust assay with high test-retest reliability.
Objective: To develop the high sensitivity Elecsys® NfL (hsNfL) assay into a Clinical trial Assay (CTA) for robust NfL determination in the GENERATION HD2 (NCT05686551) phase 2 trial of tominersen.
Methods: The Elecsys® hsNfL underwent a series of highly controlled technical experiments to meet the strict criteria for a CTA. This means the assay is robust and reliable between and across labs and can be used to support the GENERATION HD2 clinical trial via the fully-automated, IVD compliant cobas® analyzers.
Results: Method comparison study shows that the high-sensitivity Elecsys® NfL CTA has an excellent correlation to the Simoa® HD-X assay (V1) (Pearson's $R = 0.99$).
Conclusions: The technical validation of the Elecsys® NfL into a CTA assay enables continuous monitoring of NfL levels and more robust results that minimise batch effects. The increased reliability to detect associations with clinical status to provide evidence on use of the NfL in the GENERATION HD2 clinical trial.

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Partnership Enhancement Program (PEP): Humanizing Conversations around Clinical Trial Enrollment and Retention

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Cystic Fibrosis Foundation

Background: Enrollment and retention are critical for clinical trials. The relationship cultivated between

the research team, participants, and their families is paramount to successful enrollment and retention. Recognizing the significance of these relationships, the Cystic Fibrosis Foundation partnered with the Academy of Communication in Healthcare (ACH) to customize their relationship-centered communication training. This resulted in the Partnership Enhancement Program (PEP), communication training tailored to CF care and research teams.

Objective: Pilot a communication skills training to research coordinators (RC) to support enrollment and retention in CF research.

Methods: Four RC-focused PEP workshops were conducted. Each 6-hour workshop reviewed three skill sets that provide a framework for communication when working with potential or current study participants. A 90-minute follow-up session was provided 3 months post-workshop. Participants completed anonymous online surveys following the workshop and follow-up session to assess program acceptability and relevance.

Results: Training was provided to 63 RCs from 37 CF care centers. Among survey respondents (n=22), more than 80% reported being "extremely likely" to use the information they had learned in the workshops. The skills perceived to be the most useful included asking open-ended questions, responding with empathy, and checking with participants about their understanding of the clinical trial.

Conclusions: The PEP program provides a roadmap for RCs to "humanize conversations" around clinical research by sharing research information and building relationships with participants and their families. The content of the PEP program can be easily customized for various disease models and may support improved enrollment and retention in clinical trials.

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Physician Pocket Guides for Rehabilitation Therapies

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The Rehabilitation Working Group

Background: Individuals with Huntington's disease develop difficulties with functional activities, including mobility, activities of daily living, speech, language, and swallowing. Functional independence can be maintained and decline in function delayed by the timely provision of therapy services, including occupational, physical, and speech therapy. Each of these rehabilitation therapies has a unique area of practice with some overlap across providers. It can be challenging to know which problems can be addressed by a therapist and which type of therapist(s) to refer patients for care. It is also difficult to know when to refer for therapy.

Methods: To address this need, the rehabilitation therapies working group of the Huntington Study Group® created one page pocket guides to provide information regarding the types of therapy available, which therapy services each professional can provide, and when to refer for services. Each subgroup met over the course of 6 months and reviewed available literature along with convening groups to develop expert clinical recommendations when evidence was lacking.

Results: The literature in occupational therapy is minimal and expert opinion was the primary source of information. The physical therapy group was able to complete a systematic review of the literature that resulted in a clinical practice guideline, as well as the creation of a pocket guide. The speech therapy group is relying on information from an ongoing systematic review of the literature by one of its members, as well as expert opinion from their members. Each group successfully completed a pocket guide for physicians.

Conclusions: The occupational, physical, and speech therapy pocket guides provide an easy-to-use resource for healthcare providers regarding when and to whom to refer and types of services available.

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Movement to Music Telehealth Exercise Intervention: A Case Study

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Background: Impaired balance and cognitive deficits affect the mobility and independence of individuals with Huntington disease (HD). Many individuals with HD are unable to engage in exercise due to barriers such as lack of transportation and disease-specific physical, cognitive, and psychological impairments requiring caregiver support.
Objective: This pilot study aims to overcome exercise barriers for individuals with HD and their caregivers by utilizing telehealth to deliver a movement to music exercise program that combines motor and cognitive training. We report a case study from this ongoing trial.
Methods: A 59-year-old male with a Total Functional Capacity score of 11 and his care-partner underwent preassessment with motor, cognitive, and quality of life measures. They were instructed to perform the movement to music exercise program twice a week for 12 weeks.
Results: Reassessment after the intervention showed improved motor function (UHDRS® TMS score, 15 to 12; 5XSTS, 13.8 to 10.7 sec; single leg stance time 2.0 to 2.74 sec) His depression improved (PHQ-9, 13 to 7), and cognitive scale scores did not change. He stated it was easy to use and he most enjoyed dancing with his wife. They felt that his balance was better at the end of the program and stated they would continue to use it. He preferred telehealth exercise as it fit his schedule and he has anxiety being in public.
Conclusions: A telehealth movement to music exercise program was easy to use, led to improved balance and participants enjoyed that it was a partner activity.

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Supporting Huntington's Disease Families Through the Ups and Downs of Clinical Trials

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Huntington's Disease Society of America

Background: Clinical research on Huntington's Disease has progressed exponentially in recent years. As the possibility of a disease-modifying therapy grows more real for families facing HD, those who will benefit are also the ones most vulnerable to emotional distress on the road to get there.
Objective: The Huntington's Disease Society of America (HDSA) set out to understand how HD families could be best supported through the ups and downs of clinical trials.
Methods: HDSA conducted a series of interviews with members of the Huntington's Disease Coalition for Patient Engagement (HD-COPE) and an HD social worker to explore this question.
Results: Three major themes emerged from these conversations. *Engagement* is critical for participant-friendly trial design and optimal study recruitment. Supporting this finding, HDSA observed increased interactions with the clinical trials matching platform, HD Trialfinder, surrounding company efforts to present clinical trial news to the HD community. *Support* for trial participants and the HD community at large is also essential for processing negative trial news. *Education* is an important tool for managing expectations and navigating research headlines.
Conclusions: Community advocacy organizations like HDSA are key in addressing these priorities, as well as clinicians, social workers, and mental health professionals who provide services for families. While drug failures are common in clinical research, pharmaceutical companies have an opportunity to make the HD community their partners in the development of research studies to assure participant-friendly study design, and to ensure that research outcomes are communicated in a way that builds trust between stakeholders.

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Autonomic Symptoms in Huntington Disease: A Comprehensive Review

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Background: Although Huntington Disease (HD) is usually thought of as a triad of motor, cognitive, and psychiatric symptoms, recent work suggests it is a systemic illness affecting the entire body, with non-motor symptoms being more prevalent than in Parkinson Disease. Autonomic neurological symptoms (ANS) are being more frequently reported, yet a comprehensive review on this topic is lacking.

Objective: To review the available literature on ANS in HD, and to identify the current lapses in our knowledge of this topic
Methods: References were identified by searches of PubMed through February 2023. Only publications in English were reviewed. Data from 132 articles were critically reviewed, compared, and integrated.
Results: While cardiovascular disease leading to heart failure is a major cause of death in HD, premanifest HD mutation carriers also present with a higher risk of cardiovascular disease than healthy controls. Dysphagia and drooling, but also constipation and fecal incontinence, are reported more frequently in HD patients. Urinary incontinence and urgency are also reported more frequently than in healthy controls. Sexual disorders are reported in up to 85% of HD patients, with hypoactive SD being the most frequent, and SD having the highest life impact among 216 HD-related symptoms. Recent treatment guidelines did not address all autonomic symptoms, and almost all recommendations were Grade C.
Conclusions: HD can involve the ANS. Raising awareness about the autonomic symptoms' burden in HD could contribute to a new research interest in that field, as well as improved patient care.

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Enhancing Expression of C-Terminal CX3CL1 for Reducing Neurodegeneration in an HD Mouse Model

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Background: We recently discovered that the intracellular domain of CX3CL1 (CX3CL1-ct) can promote neuronal survival via altered gene transcription pathways related to TGFβ2/3 and the insulin receptor signaling[1,2]. Since Huntington's Disease (HD) patients exhibit neurodegeneration, we explored whether increased expression of CX3CL1-ct affects neuronal loss in HD mice and altered behavioral phenotypes.
Objective: This project was designed to test how overexpression of CX3CL1-ct would improve behavioral outcomes in an HD YAC128 mouse model.
Methods: To overexpress CX3CL1-ct in this HD model, we first crossed YAC128 mice with transgenic mice overexpressing the CX3CL1-ct gene, driven by the CAMKIIA promotor. Starting at the age of 3-month-old, mice of both sexes underwent behavioral tests, including the open-field, Y-maze, and Rotarod behavioral paradigms every three months.
Results: We found significant improvement in Rotarod performance in mice overexpressing the CX3CL1-ct transgene compared to control littermates at 6- and 9-months of age ($p<0.01$, 2-way ANOVA), as well as improved working memory on the Y-maze at 9-months and 12-months ($p<0.05$, 2-way ANOVA). Time spent in the open portion of the elevated zero maze at 12-months was significantly higher in the CX3CL1-ct transgene overexpression group ($p<0.05$, 2-way ANOVA), suggesting reduced anxiety.
Conclusions: This study provides the first evidence that overexpression of the CX3CL1-ct in YAC128 HD mice ameliorates behavioral deficits. Future studies are planned to evaluate the potential role in histopathological outcomes as well as attempting to elucidate the underlying mechanism in cell culture. Together, enhancing expression of CX3CL1-ct is likely a novel approach for HD treatment.

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Beta-Blocker Use Is Associated with Delayed Onset and Progression of Huntington's Disease

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Background: Patients with Huntington's Disease (HD) have enhanced sympathetic output that correlates with HD symptoms. The mechanism of action of Beta-blockers (b-blocker) may, therefore, play a therapeutic role in HD.
Objective: This study investigated the therapeutic potential of beta-blockers in HD.

Methods: We identified subjects with pre-manifest HD (preHD) using a b-blocker and propensity-score-matched them to non-b-blocker users. Cox regression survival analyses compared the hazard of receiving a motor diagnosis between these groups. We then identified patients with early motor-manifest HD (mmHD) who were using a b-blocker and matched them to non-users. Linear mixed effects regression models compared the annualized rate of change in Total Motor Score (TMS), Total Functional Capacity (TFC), and Symbol Digit Modalities Test (SDMT) between groups.
Results: The annualized hazard of receiving a motor diagnosis in preHD subjects was lower amongst b-blocker-users (n=174) compared to non-users (n=174) (HR = 0.66, 95% CI [0.46 – 0.94], p=0.022). Subjects with mmHD who were using a β-blocker (n=149) had a slower mean annualized worsening (increase) in TMS (Mean Difference [MD] = -0.45, 95% CI [-0.85 – -0.06], q=0.025), TFC worsening (decrease) (MD = 0.10, 95% CI [0.02 – 0.18], q=0.025), and SDMT worsening (decrease) (MD = 0.33, 95% CI [0.10 – 0.56], q=0.017) compared to matched non-users (n=149).
Conclusions: β-blockers were associated with a significantly lower risk of receiving a motor diagnosis in preHD and were associated with significant slowing of clinical progression in mmHD. Autonomic dysfunction may be a key, modifiable pathologic feature of HD that impacts progression of the disease.

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A Novel Scale to Assess Motor Progression in Juvenile-Onset Huntington's Disease: An Enroll-HD Analysis

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Background: Juvenile-onset Huntington's disease (JOHD) is characterized by a unique motor phenotype relative to patients with adult-onset Huntington's Disease (AOHD).
Objective: This study characterized motor progression of JOHD to propose improved outcome measures for this group.
Methods: We used linear mixed effect regression models to compare progression of the Unified Huntington's Disease Rating Scale (UHDRS®) Total motor Score (TMS) and the chorea score between patients with JOHD and AOHD. We then evaluated all 31 subscales that make up the UHDRS® over time within patients with JOHD to identify measures that may be used to track motor progression most reliably.
Results: The JOHD cohort had faster TMS progression compared to AOHD (p=0.006) but no group difference in the rate of change of chorea. Patients with JOHD did not show significant change in any of the chorea subscales. The subscales that changed most reliably over time amongst patients with JOHD were dysarthria, upper extremity dystonia, tandem walking, gait, bilateral pronate/supinate, bilateral finger-tapping, and tongue protrusion. When these subscales were summed, they progressed at a faster rate (7.07%, 95% CI [5.96 – 8.18]) than the TMS (4.92%, 95% CI [3.95 – 5.89]).
Conclusions: While the TMS changes at a significant rate in JOHD subjects, the inclusion of specific subscales increase variability. A JOHD-specific scale performed better at tracking motor progression relative to the TMS. This scale may improve clinical care for patients with JOHD and allow for the development of more efficient clinical trials.

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Racial Differences in the Presentation and Progression of Huntington Disease

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Background: In recent years, the number of people seeking care for Huntington disease (HD) has increased. HD is an autosomal dominant neurodegenerative disease that predominantly impacts a Caucasian population, but few efforts have explored racial differences in the presentation and progression of HD.

Objective: To assess racial differences in presentation and progression of HD across race groups using the Enroll-HD longitudinal observational study.
Methods: Enroll-HD is a global longitudinal observational study of HD participants. We identified 104 Asian participants and used propensity score matching for CAG age product (CAP) score, and age, to identify 208 White, 208 Hispanic, and 104 Black participants. Progression over time was analyzed by comparing each minority race to White participants as a base group. Cohen's *d* showed the effect size between race groups for each cognitive, functional, and motor score.
Results: Black participants were more severe at baseline across all measures when compared to White participants. The largest effect size (d>0.49) was similar between Black and White participants on cognitive and motor scores. In a longitudinal model that controlled for age and CAP score, there were no significant differences between groups assessing progression over time.
Conclusions: Black participants presented with a greater disease burden at baseline in comparison to other races, but there are no clear distinctions in progression over time. We interpret these results as evidence of a selection bias to more severe clinical symptoms in Black participants. We discuss the need for greater efforts to recruit underrepresented minorities in clinical studies of HD.

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Melatonin for Huntington Disease (HD) Gene Carriers with HD-Related Sleep Disturbance - a Pilot Study

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Background: Sleep disturbance is a prevalent but underreported feature of Huntington Disease (HD). Possible causes include circadian rhythm dysfunction and altered melatonin levels. Although melatonin is an effective treatment for circadian dysregulation, its efficacy in HD-related sleep disorders is unknown.
Objective: This double-blind, randomized, placebo-controlled, cross-over trial (NCT04421339) was designed to evaluate the efficacy of melatonin (5 mg) on HD patients' sleep quality.
Methods: Eligible adults aged 18 to 75 years with sleep disturbance (cut-off score of 5 on the Pittsburgh Sleep Quality Index [PSQI]) were recruited. At baseline, week 5 (cross-over visit), and week 9 (final visit), participants completed the PSQI, HD Sleep Questionnaire (HD-SQ), Epworth Sleepiness Scale (ESS), Montreal Cognitive Assessment (MoCA), Neuro-QoL™ v2.0 Cognitive Function, Neuropsychiatric Inventory Questionnaire (NPI-Q), Hospital Anxiety and Depression Scale (HADS), Unified Huntington Disease Rating Scale (UHDRS®) motor and Total functional Capacity (TFC), and Clinical Global Impression (CGI).
Results: Fifteen patients with a mean age of 46.53 ± 13.92 (7 females, 8 males) were recruited. The primary endpoint (PSQI components) did not show any significant difference between melatonin and placebo, nor did the other sleep indices (ESS and HD-SQ). Following melatonin therapy, the neuropsychiatric symptoms (NPI-Q and HADS), cognitive function (Neuro-QoL and MoCA), and motor/functional measures were comparable to placebo.
Conclusions: Melatonin was not significantly different from placebo. Given the mixed results of research on circadian melatonin release in HD, it would be beneficial for future studies to consider alternative melatonin dosages, different disease stages, and a larger sample size.

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Patient and Caregiver Survey Reveals Potential for Improvement in Timeliness of Approval of Social Security Disability Compassionate Allowance Claims

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Background: Social Security disability (SSD) is a necessity for individuals impacted by Huntington's

disease. Unfortunately, the SSD process is incredibly difficult for HD-impacted individuals and families, even though the Social Security Administration (SSA) has rules in place to help. HD is classified as a Compassionate Allowance (CAL) condition, meaning all HD claims should be flagged for CAL and the review process should be expedited. SSD applicants should get a decision in less than 6 months, with an average timeline of 3–4 months for a decision.

Objective: To highlight that HD individuals are unduly impacted by the SSD process, and claims are not correctly processed.

Methods: Nine question online survey was developed and promoted through multiple channels including emails to contacts in the HDSA database and standard social media platforms.

Results: 450 individuals responded to the survey. 329 indicated they filed a disability claim for themselves or a loved one. 255 continued with the survey. Only 22% responded the claim was flagged for CAL. Less than 50% of respondents reported claim was approved within the CAL timeframe.

Conclusions: Results provide an opportunity to bring systemic change to the Social Security Administration. Specifically, to notify applicants about their rights for CAL and to use claim reviewers with clinical expertise in Huntington's Disease.

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Using the Computerized Test of Information Processing (CTiP) to Explore the Presence of Bradyphrenia in Huntington's Disease

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Background: Bradyphrenia, best thought of as the mental equivalent of bradykinesia, has been described in several disorders of the brain including Parkinson's disease and schizophrenia; however, little is known about this phenomenon in Huntington's Disease (HD).

Objective: The aim of this study was to investigate the presence of bradyphrenia in HD using the Computerized Test of Information Processing (CTiP), an easy to administer and objective task that assesses cognitive processing speed with increasing task complexity.

Methods: This study included 216 participants: Huntington's Disease Integrated Staging System (HD-ISS) Stage 0 [n=28], Stage 1 [n=35], Stage 2 [n=61] and Stage 3 [n=48], and healthy controls (HC) [n=44]. The CTiP incorporates three subtests: Simple Reaction Time (SRT), which assesses baseline motor function; Choice Reaction Time (CRT), with an added decisional component; and Semantic Search Reaction Time (SSRT), with an added conceptual component. SRT scores were subtracted from CRT and SSRT scores to establish a motor-corrected measure of central conduction time, which was used to operationalize bradyphrenia.

Results: HD-ISS and HC within-group reaction times differed significantly when comparing motor-corrected CRT vs. SSRT (all *p*s<0.0001). Furthermore, the magnitude of these differences increased with HD disease stage (p<0.0001). An ROC analysis determined that motor-corrected within-subject differences significantly distinguished Stage 2+3 from Stage 0+1 (AUC=0.72, p<0.0001).

Conclusions: We report evidence of bradyphrenia in HD that increases with disease progression. This processing deficit, which can be quantified using the CTiP, has the potential to greatly impact HD daily life and warrants additional research.

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Mapping Neurodegeneration across the Huntington's Disease Spectrum: A Five-year Longitudinal Analysis of Plasma Neurofilament Light

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Background: We and others have previously highlighted neurofilament light (NfL), a protein associated with axonal injury, as a potential biomarker for

Huntington's Disease (HD), using cross-sectional analyses.
Objective: Our aim was to investigate how longitudinal trajectories of plasma NfL relate to disease stage and symptom presentation across the HD spectrum.
Methods: 111 participants representing HD-Integrated Staging System (HD-ISS) Stage 0 [n=15], Stage 1 [n=26], Stage 2 [n=19], Stage 3 [n=21], and healthy controls (HC) [n=30] were included in this study. Plasma NfL trajectories were examined using Mixed Linear Modeling (MLM) and Change-Point analyses; associations with symptom presentation were assessed using Spearman's rho correlations.
Results: For the MLM of plasma NfL levels across time, the coefficients for HD-ISS category (β=34.69, $p<0.001$) and HD-ISS category*time (β=6.95, $p=0.002$) were significant. The plasma NfL rate of change also varied significantly over time ($p=0.02$; plasma NfL pg/ml/year for Stage 0=7.09, Stage 1=8.48, Stage 2=13.68, Stage 3=51.82) with a change-point analysis indicating a significant inflection point in Stage 3. Moreover, a post-hoc MLM analysis restricted to ≤Stage 2 participants demonstrated a linear rate of change for plasma NfL across time. Plasma NfL levels were correlated with SDMT in ≤Stage 2, and SDMT and TMS in Stage 3 (all *p* values <0.01).
Conclusions: Our findings suggest that plasma NfL levels increase linearly across the earlier stages of disease, during which time they primarily correlate with cognitive performance; thereafter, plasma NfL levels correlate with both cognitive and motor measures. These findings reaffirm the potential for NfL as a prognostic marker in HD.

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Balance Impairment May Be Useful in Tracking the Transition from Premanifest to Manifest HD

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Background: In Huntington's Disease (HD), balance impairment can begin prior to overt motor symptom onset. The BTrackS™ is a simple balance device that uses center of pressure to assess Total body Sway (TBS).
Objective: Our objectives were to examine whether the BTrackS™ can 1) distinguish between normal controls (NC) and pre-manifest (PM) HD and 2) identify an association between TBS and predicted years to HD onset in PM subjects.
Methods: We assessed NC [n=38], PM [n=91], and HD [n=88] subjects using the BTrackS™. The PM cohorts were further stratified by CAPs scores as low [n=28], medium [n=21], and high [n=42] likelihood of progressing to manifest HD [2]. Subjects were given ten-second, eyes open trials. A one-way ANCOVA adjusting for age was used to compare TBS among the cohorts. TBS and predicted years to onset were correlated using Spearman's rho.
Results: Not surprisingly, statistically significant differences in TBS were observed between NC and HD subjects ($p < .001$). Importantly, however, differences were also identified between NC and High PM and between Low and High PM cohorts (both $p < .01$). Within the PM group, there was a significant correlation between TBS and predicted years to manifest HD onset ($r = -.35$, $p < .001$).
Conclusions: We conclude that subtle balance impairment, as measured using the BTrackS™ Balance Device, becomes apparent prior to discernable motor onset and may be useful in tracking the transition from PM to manifest HD.

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A Clinically Integrated HD Biobank at the UBC Centre for Molecular Medicine and Therapeutics

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Genetic and biological studies of Huntington disease (HD) require high-quality samples from HD patients and families, and associated phenotype data from formal clinical assessments. The HD Biobank at the UBC Centre for Molecular Medicine and Therapeu-

tics (UBC HD Biobank) is one of the largest HD biobanks in the world, comprising more than 20,000 DNA samples and 1500 individual brain and peripheral tissue samples drawn from over 5000 HD subjects and family members. A majority of HD subjects represented in the UBC HD Biobank have been seen at our affiliated HD clinic, the UBC Centre for Huntington Disease, often with successive generations returning for care. To maximize the impact of these valuable HD Biobank donations for HD research, we have developed a formal integration of the UBC HD Biobank with the UBC Centre for HD, encompassing recruitment, consenting, sample donation, and cataloging of participant clinical data on an ongoing basis. In addition to integration with local HD clinic and pathology services, we have developed a dedicated sample collection network with streamlined approaches to facilitate donations Canada-wide. Thus far, we have expanded our pathology and tissue collection network from British Columbia to include Alberta, Saskatchewan, Manitoba, and Ontario, with planned expansion to remaining Canadian provinces. In 2023, the rate of tissue donations to the UBC HD Biobank has increased over 4x compared to previous years. We have made this integrated resource available to the HD research community with formal options for worldwide collaborative use.

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An AI-assisted Video Telemedicine System for Assessment of Movement Disorder in HD Patients

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Background: Huntington's disease (HD) is a rare chronic progressive neurodegenerative disease and assessment of movement disorder is of great significance for the care of HD. Development of a convenient and effective method for clinical analysis of HD severity is in urgent need.
Methods: In the present study, all participants were required to provide 6 1-minute-videos, demonstrating patients in seated, standing, and walking positions. 27 patients participated in the video reliability test to evaluate the consistence of scores derived from videos taking at home and scores derived in the clinic visit. 48 HD patients and 48 healthy controls were enrolled in the Artificial intelligence (AI) study. Firstly, we designed a 3D convolutional module based on channel-spatial attention to extract data features. We then used an excitation-based 3D residual convolution module for feature learning. Finally, we used a fully connected layer based on channel-spatial attention to complete feature compression and obtain video classification results. An AI-assisted video telemedicine system was developed based on these results.
Results: The consistency between video analysis and in-person visit was excellent (r = 0.969, P <0.001). The ACC of our AI model to distinguish HD patients and Healthy controls was 85%.
Conclusions: Our video telemedicine platform is a feasible and reliable option for HD patient care. Our AI models further facilitate HD care, especially at the remote area.

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Epilepsy in Pediatric-onset Huntington's Disease

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Background: Seizures can be a presenting symptom of pediatric-onset Huntington's disease (PoHD), and epilepsy occurs in up to half of children with PoHD. This is in stark contrast to adult-onset HD, where the frequency of seizures is similar to the general public (~1%).
Objective: We present a case report and review of the literature on epilepsy in PoHD to increase awareness and highlight important areas of future research.
Methods: Chart review and review of available literature on epilepsy in PoHD was conducted. Parent consent was obtained.
Results: A 10-year-old boy with language delay, oral motor dysfunction, and developmental regression presented with a first lifetime seizure. Initial routine electroencephalogram (EEG) showed parietal-occipital spike-and-slow wave complexes. Genetic testing revealed a pathogenic *HTT* allele with 88 repeats, which was anticipated from his father's allele with 44 repeats. The boy was started on levetiracetam, and then valproic acid was added. History alone could not differentiate abnormal movements

from seizures. Overnight continuous video EEG monitoring demonstrated epileptic myoclonic jerks. Clobazam was added nightly to target both disordered sleep and myoclonic jerks.
Conclusions: Continuous video EEG monitoring is a key tool for differentiating a movement disorder from seizure, and an epilepsy monitoring unit stay can be helpful to monitor medication tolerability, efficacy, and effects on comorbidities such as sleep, balance, and mobility. Valproate is the most common medication reported, but with newer generations of anti-seizure medications, understanding current provider practices will be helpful. Overall, epilepsy is an underappreciated feature of PoHD but is important to recognize.

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Real-world Experience on the Management of Deutetrabenazine in Patients with Huntington's Disease in CHDN Guangzhou Center

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Background: Huntington's disease (HD) is a rare neurological disorder that can lead to uncontrolled movements, cognitive and psychiatric problems. Deutetrabenazine (DTBZ) is a vesicular monoamine transporter type 2 inhibitor and is recently available in China. However, the information for the application of DTBZ is scarce in Asian population. Therefore, a real-world experience on the management of DTBZ is necessary.
Methods: In total 118 patients from CHDN Guangzhou Center, seventeen patients were successfully enrolled from March 2021 to June 2022. The primary outcome is the change from the baseline of chorea score, and the secondary outcomes are as follows: Patient Global Impression of Change (PGIC), Clinical Global Impression of Change (CGIC), and Adhesiveness.
Results: The mean (SD) daily dose of DTBZ was 11.29 (7.67) mg. Patients had a mean –1.41(95% confidence interval, –2.46 to –0.37) improvement in total maximal chorea score. 13 patients (76.47%) reported treatment success by the PGIC and CGIC. For the adherences, 7 of 17 patients (41.17%) continue the DTBZ treatment. For those 10 patients who discontinue the treatment, 1 patient died because of other disease and 8 patients had no medical insurance reimbursement and could not afford the medicine, all of them only took 6mg doses of DTBZ. 4 patients (23.53%) experienced any AE that was assessed as being at least possibly related to the DTBZ.
Conclusions: DTBZ treatment could reduce chorea and improve quality of life, but cost was a barrier to treatment for many patients.

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Preliminary Results from the Pilot First-in-human Study of ER2001, an Innovative Treatment for Huntington's Disease Using In Vivo Self-assembled siRNA

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Background: ER2001 is a genetic circuit (plasmid) encoding both a neuron-targeting rabies virus glycoprotein (RVG) tag and an HTT siRNA. This circuit is able to reprogram liver cells to transcribe and self-assemble HTT siRNA into RVG-tagged exosomes after intravenous administration. The RVG guided HTT siRNA is further delivered through the exosome-circulating system to the cortex and striatum.
Objective: To evaluate the safety and tolerability of ER2001 in patients with early manifest HD, including the pharmacokinetics (PK) of ER2001 in plasma and the exposure of ER2001 in cerebrospinal fluid (CSF).

Methods: This open label, single center pilot study evaluates a single dose of ER2001 followed by multiple doses in eligible patients with early manifest HD. A modified 3 plus 3 dose-escalation design is employed with escalating rules set according to the incidence of dose-limiting toxicity (DLT), including 0.04, 0.08, 0.16, and 0.32 mg/kg dose cohorts. The safety, PK, PD, and clinical outcomes, such as UHDRS®, mHTT, and NfL, will be assessed. Participants will receive a total of 8 intravenous injections of ER2001, and the treatment period of 14 weeks will be followed by an observation phase of 84 days after the last injection.
Results: We have enrolled 4 patients up to now and revealed a total of 9 mild-moderate AEs in 2 female patients. None of the adverse events are related to ER2001. No serious adverse event is present.
Conclusions: The safety review committee (SRC), with access to all unblinded data, thoroughly reviewed the safety data and concluded that to date no safety signals of concern have emerged. (Safety, PK, PD, and clinical outcomes will be updated once available.)

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Patient Functioning and Cognitive Performance among individuals with Huntington's Disease: A Real-world Study

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Background: Individuals with Huntington's Disease (HD) experience significant difficulties in cognitive abilities and daily functioning, even at early stages of the disease.
Objective: To understand the holistic impact of HD on patients' lives using real-world data (RWD).
Methods: Adults with an HD diagnosis or mutant huntingtin expansion gene were enrolled in the PicnicHealth platform (June 2022–April 2023), which aggregates data on clinical history and demographic information from medical records and administers patient-reported outcomes surveys. Results from enrollment surveys are reported.
Results: 365 HD patients were included (mean age 45.9±13.4 years, 89% White, 66% female). Of those who completed the Unified HD Rating Scale, Total Functional Capacity (UHDRS®-TFC) (N=269), 61% had TFC =13-7. Lower TFC scores were associated with poorer performance on the Digital Symbol Substitution Test (DSST) (range: 0.13-0.42), EQ-5D Visual Analogue Scale (range: 42.3-80.6) and HD Everyday Functioning Scale-Short Form (Hi-DEF-SF) (range: 23.3-70.8), indicating lower cognitive abilities, lower QoL, and greater functional deficits with increasing HD severity. Over 69% of patients reported difficulty on all items of Hi-DEF-SF. Percent of patients reporting difficulty in getting thoughts across in group conversations and in multistep tasks was 59% and 47% respectively among TFC=13-11; and 92% and 91% respectively among TFC=10-7. Among employed patients (N=100), the mean overall work impairment as measured by the Work Productivity and Activity Impairment-HD score was 25%.
Conclusions: RWD shows that cognitive impairment in HD can significantly affect work, independence, and executive functioning abilities. Further analyses will explore additional outcomes, including symptom burden, treatment patterns, and costs.

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

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Summary: Here, we describe the design of a Phase 2, randomized, placebo-controlled study of PTC518, a novel, oral splicing modifier in development for the treatment of Huntington's disease. In this study, participants will receive PTC518 5 or 10 mg once daily for 12 months. Based on ongoing data from these dose levels, a higher dose level has been deemed safe to proceed by an independent Data and Safety Monitoring Board. PTC518 affects splicing of huntingtin gene (*HTT*) pre-mRNA, leading to mRNA degradation and lowering of huntingtin levels, as demonstrated in a recent Phase 1 study.

Background: Huntington's disease (HD) is caused by expansion of cytosine-adenine-guanine (CAG) trinucleotide repeats in the huntingtin gene (*HTT*). The mutant protein is ubiquitously expressed and drives HD pathogenesis through a toxic gain-of-function mechanism. Animal models demonstrate that reducing huntingtin protein (HTT) levels alleviates HD symptoms. PTC518 is a splicing modifier that promotes the inclusion of a pseudoexon (psiExon) containing a premature stop codon, leading to *HTT* messenger RNA degradation and lowering of HTT levels. Results of a Phase 1 study demonstrated PTC518's ability to lower HTT levels in healthy volunteers, supporting Phase 2 evaluation.
Objective: The goal of PIVOT-HD (NCT05358717/2021-003852-18), a 12-month, placebo-controlled, double-blinded study, is to evaluate safety, efficacy, pharmacology, and biomarker effects of PTC518 in participants with HD.
Methods: Approximately 252 participants ≥25 years old, with genetically-confirmed HD (40–50 CAG repeats, inclusive) and Stage 2 or Mild Stage 3 HD (per the HD Integrated Staging System), will be enrolled. Primary outcome measures: safety profile of PTC518 through Month 18 and change from baseline in blood total HTT at Month 3. The effects of PTC518 on blood and cerebrospinal fluid biomarkers will also be observed. Participants will be randomized 1:1 to Part A/D (5 mg PTC518 once-daily [QD]) or Part B/E (10 mg PTC518 QD) based on their HD staging and then randomized 2:1 within each part to PTC518 or placebo. Based on the findings of Parts A and B, a higher dose level has been deemed safe to proceed by an independent Data and Safety Monitoring Board.
Summary: Here, we describe the design of a Phase 2, double-blind, randomized extension study of PTC518. The PIVOT-LTE study is enrolling participants who have completed the 12-month PIVOT-HD study. PTC518 is a novel, oral splicing modifier in development for the treatment of Huntington's disease. PTC518 affects splicing of huntingtin gene (*HTT*) pre-mRNA, leading to mRNA degradation and lowering of huntingtin levels, as demonstrated in a recent Phase 1 study.
Background: Huntington's disease (HD) is caused by expansion of cytosine-adenine-guanine (CAG) trinucleotide repeats in the huntingtin gene (*HTT*). The mutant protein is ubiquitously expressed and drives HD pathogenesis through a toxic gain-of-function mechanism. Animal models demonstrate that reducing huntingtin protein (HTT) levels alleviates HD symptoms. PTC518 is a splicing modifier that promotes the inclusion of a pseudoexon (psiExon) containing a premature stop codon, leading to *HTT* messenger RNA degradation and lowering of HTT levels. Participants enrolled in PIVOT-LTE will have completed a 12month Phase 2 study of PTC518, PIVOT-HD (NCT05358717/2021-003852-18), and will continue in PIVOT-LTE for extended treatment with PTC518.
Objective: The goal of PIVOT-LTE is to evaluate long-term safety, efficacy, pharmacology, and biomarker effects of PTC518 in participants with HD.
Methods: All participants who completed PIVOT-HD are anticipated to be enrolled in PIVOT-LTE. Participants will have completed treatment with PTC518 or placebo in PIVOT-HD and will have the option to roll over into this extension study. The primary outcome measures are long-term safety profile of PTC518 through Month 30 and change from baseline in blood total HTT over time. The effects of PTC518 on blood and cerebrospinal fluid biomarkers will also be determined. All participants will receive PTC518 in this study at the same dose level they received in PIVOT-HD; participants who received placebo in PIVOT-HD will be randomized 1:1:1 to receive PTC518 5 or 10 mg or a potential higher dose once daily.

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PIVOT-LTE: A Phase 2, Double-Blind, Randomized Extension Study to Evaluate the Long-Term Safety and Efficacy of PTC518 in Participants with Huntington's Disease

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

Amy-Lee Bredlau, Brian Beers, Anu Bhattacharyya, Jonathon Kaiser, Ronald Kong, Allan Kristensen, Lee Golden

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Summary: Here we present a planned interim data readout from the ongoing Phase 2, placebo-controlled study of PTC518 in participants with Huntington's Disease (HD) (PIVOT-HD). PTC518 is a novel, oral splicing modifier in development for the treatment of HD. The interim data has shown PTC518 dose-dependently lowered huntingtin protein levels in whole blood. PTC518 treatment was also demonstrated to be safe and well-tolerated.

Background: Huntington's disease (HD) is caused by expansion of cytosine-adenine-guanine (CAG) trinucleotide repeats in the huntingtin gene (*HTT*). The mutant protein is ubiquitously expressed and drives HD pathogenesis through a toxic gain-of-function mechanism. Animal models demonstrate that reducing huntingtin protein (HTT) levels alleviates HD symptoms. PTC518 is a splicing modifier that promotes the inclusion of a pseudoexon (psiExon) containing a premature stop codon, leading to *HTT* messenger RNA (mRNA) degradation and lowering of HTT levels.

Objective: The objectives of this planned interim data readout are to evaluate the safety and biomarker effects of PTC518 in participants with HD from PIVOT-HD, an ongoing Phase 2, placebo-controlled study.

Methods: Participants with HD were randomized to receive PTC518 5 or 10 mg or placebo once daily for 12 months. Interim safety and biomarker data from the 12-week portion of PIVOT-HD will be reported.

Results: Thirty-three participants were included in this planned interim readout. PTC518 dose-dependently lowered blood mHTT protein, total HTT, and blood *HTT* mRNA levels at week 12. PTC518 exposure ratios in the cerebrospinal fluid (CSF) were consistent with or higher than the plasma unbound drug levels. Finally, PTC518 treatment was well tolerated, with no treatment-related serious adverse events and no reports of peripheral neuropathy or dose-limiting toxicities. There were no CSF neurofilament light chain protein treatment-related spikes.

Conclusions: These interim results demonstrate that PTC518 is a potential therapeutic for the treatment of HD. PTC is actively enrolling participants with HD in PIVOT-HD (NCT05358717/2021-003852-18).

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Alterations in Cerebrospinal Fluid Urea Occur in Late Manifest Stage Huntington's Disease

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Background: Huntington disease (HD) is a neurodegenerative disorder caused by expanded cytosine-adenine-guanine (CAG) repeats in the Huntingtin gene, resulting in the production of mutant huntingtin proteins (mHTT). Previous research has identified urea as a key metabolite elevated in HD animal models and post-mortem tissues of HD patients. However, the relationship between disease course and urea elevations, and the molecular mechanisms responsible for these disturbances remain unknown.

Objective: To better understand the timing of alterations in the urea cycle throughout the disease.

Methods: We completed a global metabolomic profile of cerebrospinal fluid (CSF) from individuals who were at several stages of the disease: pre-manifest (PRE), manifest (MAN), and late manifest (LATE) HD participants, and compared to controls.

Results: Approximately 500 metabolites were significantly altered in PRE participants compared to controls, although no significant differences in CSF urea or urea metabolites were observed. CSF urea was significantly elevated in LATE participants only. There were no changes in the urea metabolites citrulline, ornithine, and arginine; however, we did observe changes in acetate, creatinine, 4-acetamidobutanoate, and 4-aminobutyraldehyde, which are indirect contributors to the urea cycle.

Conclusions: Overall, our study confirms that CSF elevations occur late in the HD course, and these

changes may reflect accumulating deficits to cellular energy metabolism. A more in-depth investigation into these biochemical compounds may yield novel biomarkers for pre-motor manifest patients, which can be used in the next phase of clinical trials for HD.

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Psychiatric Symptoms and Adverse Childhood Experiences in Youth at Risk for Huntington Disease

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Background: Children and adolescents at risk for Huntington disease (HD) are subject to chronic stress and exhibit elevated symptoms of depression and anxiety. However, the contributions of genetic risk vs. environmental factors to the development of psychiatric symptoms remain unclear.
Objective: To characterize early psychiatric symptoms among children ages 10-18 at risk of developing HD and to investigate the relationship between these symptoms and adverse childhood experiences.
Methods: Seventeen children at risk for HD (*M*age 13.9, *SD* 2.9) and twenty healthy community controls (*M*age 12.5, *SD* 1.7) completed the ASEBA Youth Self Report (YSR) and Childhood Trauma Questionnaire (CTQ).
Results: Children at risk for HD scored significantly higher than community controls (HC) on multiple subscales of the YSR, including Anxious/Depressed (M_{HD} 59.8, M_{HC} 54.3, p = 0.04) Withdrawn/Depressed (M_{HD} 61, M_{HC} 54.8, p = 0.02), Social Problems (M_{HD} 62.2, M_{HC} 55.8, p = 0.02), Thought Problems (M_{HD} = 60.2, M_{HC} 55, p = 0.03), Attention Problems (M_{HD} 63, M_{HC} 55.6, p = 0.007), and Internalizing Problems (M_{HD} 59.6, M_{HC} 49.5, p = 0.007). CTQ scores were not significantly different between groups (M_{HD} 37.2, M_{HC} 33.9, p = 0.4). CTQ scores were significantly correlated with YSR scores in both groups.
Conclusions: Children at risk for HD show significant elevations in psychiatric symptoms compared to community controls as young as age 10 despite similar frequencies of adverse childhood experiences. Further research should investigate this relationship longitudinally in a larger cohort.

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Acceptability of Web-Based Interpretation Bias Training to Reduce Anxiety in Huntington's Disease

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Background: Anxiety symptoms are common for individuals with Huntington's disease (HD), yet undertreated. Existing in-person and pharmacological therapies are inadequate to reduce this treatment gap. Digital mental health interventions, such as cognitive bias modification for interpretation bias (CBM-I), offer a potential method to reduce anxiety in a way that is effective and accessible for people with HD.
Objective: The present pilot study aimed to assess the acceptability and user experience of an existing web-based CBM-I program for anxiety in people with HD.
Methods: We recruited individuals with HD and anxiety symptoms (n = 21) to complete a web-based CBM-I program (MindTrails) with five weekly training sessions and to provide feedback about their experience in a qualitative interview.
Results: Attrition was primarily related to participant burden at enrollment. Of those who began the first session (n = 16), 75% completed all five sessions. Two thirds of completers improved in self-reported anxiety symptoms from pre- to post-treatment. In qualitative interviews (n = 10), most participants found the program enjoyable and useful but offered recommendations to enhance relevance and ease-of-use for people with HD.
Conclusions: These findings suggest that web-based CBM-I may be acceptable for adults with HD and anxiety but that the program and study procedures require adaptation to improve accessibility and relevance to HD. Our next step is to tailor the inter-

vention for people with HD, incorporating user-centered design to address needs identified by this population.

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Enroll-HD Study Status

Enroll-HD Platform Team

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

As of July 1, 2023, 29,930 participants have been recruited from 186 sites (157 are active) in 23 countries. 21,348 of those are still current (i.e., no mortality/end form), and 15,984 are active (i.e., have not missed two or more visits).

Recoded data and biosamples are made available to researchers. The data and biosamples collected in Enroll-HD have led to significant scientific breakthroughs with over 350 projects and 120 publications. The sixth periodic dataset was released in January 2023 and contains data from 25,550 participants and 95,040 visits.

The Functional Rating Scale 2.0 (FuRST 2.0) and a Sleep Assessment are being added to Enroll-HD's extended assessment battery at the sites in the United States. These additional assessments will be available to other countries in the future.

An increasing number of clinical trials/studies are utilizing at least one area of Enroll-HD platform support, such as site feasibility, guidance on study design, potentially eligible participant listings, study set-up support, monitoring and data management.

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

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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. This study aims to evaluate the clinimetric properties for two such measures: the HD Structured Interview of Function (HD-SIF) and HD Clinical Status Questionnaire (HDCSQ). Both assessments are administered to a companion either in-person or remotely (i.e., by phone contact with the companion), and the properties of these tests are being evaluated in a two-part study using the methods of Classical Test Theory (CTT) and Item Response Theory (IRT).

Methods: 170 dyads of people with Huntington's disease and their Companion Participants will be enrolled. The study includes two parts. In Part 1, we are using the methods of CTT to evaluate the HD-SIF, a structured interview designed to gather information for making ratings on the UHDRS® '99 functional scales (TFC, FAS, and IS). In Part 2, we are using 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.

Current Status and Outlook: Four US sites have recruited 16 dyads in Part 1 and 10 dyads in Part 2. Preliminary results from Part 1 will be available in the first quarter of 2024. Part 2 began in June 2022 with preliminary results expected in the first quarter of 2025. 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.

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Psychiatric Symptoms in Adolescent and Young Adults with Huntington's Disease

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Background: Psychiatric symptoms are a core clinical feature of Huntington's disease (HD), including mood symptoms and risky behaviors. Early identification of problems is critical to reduce the negative impact on functioning, yet few studies have assessed psychiatric symptoms of children and adolescents at risk for HD.
Objective: To compare the psychiatric symptoms of gene-expanded (GE) and gene-not-expanded (GNE) adolescents and young adults using a multi-informant approach.
Methods: The sample included 110 participants (ages 10-39) with (n=71) and without (n=39) the *HTT* gene expansion and 85 other informants (i.e., HD parent, parent without HD, spouse). Participants reported on seven symptom scales and two composites using the age- and informant-appropriate Achenbach System of Empirically Based Assessment measure. Consenting procedures were followed to obtain saliva samples for blind genetic testing as described previously.
Results: There were no statistically significant group differences based on self-report on any psychiatric scale or composite. There were significant group differences on four symptom scales based on other informant reports such that GE had *greater* symptoms than GNE on depression, attention, aggression, and rule-breaking. No significant differences were reported on the remaining scales and composites.
Conclusions: Findings suggest adolescents and young adults with *HTT* gene expansion may experience greater psychiatric difficulties compared to GNE individuals. Importantly, differences were only evident from other informant reports, which had a reduced sample size; there were no group differences based on self-reports. Findings highlight the need to obtain collateral information about psychiatric symptoms in an at-risk sample.

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Personalized Psychopharmacology in the Management of Neuropsychiatric Symptoms of Huntington's Disease

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Background: Neurobehavioral symptoms in Huntington's disease (HD) occur early in the course of the disease and tend to be frequent and complex. Although there is currently no cure for HD, it is a misconception that the symptoms are untreatable.
Objective: To investigate the in-practice utility of guided psychopharmacology in patients with HD.
Subjects & Methods: Demographics, genetics and pharmacogenomics, as well as neurobehavioral parameters were analyzed in 36 patients with symptomatic HD evaluated at between 2019 and 2023. Medication changes were guided by pharmacokinetic genotypes: CYP1A2; CYP2B6; CYP2C19; CYP 2C9; CYP 2D6, CYP 2A4; CYP 3A5; UG 1A4; UCT2B15, as well as pharmacodynamics genotypes: HTR2A; SLC6A4. Additionally, medication modifications were guided by HLA-A and HLA-B genotype.
Results: Patients were evaluated at baseline and 8 weeks after implementation of changes guided by pharmacogenomic testing. Only 17% of patients didn't require changes in either their type or dose of medication. Change in the type of medication was required in 69% of patients, and augmentation with another medication in 59% of patients. 67% of patients reported improvement in symptom management after implementing medication changes. Only 14% of patients reported overall worsening, and no noticeable changes were reported in 19%. Guided psychopharmacology was beneficial in the management of all neuropsychiatric symptoms assessed, with the largest effect in the treatment of psychosis. Compulsions and obsessive thoughts were the most resistant to change. CYP2D6 variation determined VMAT2 dose for chorea management (higher target dose in ultra-rapid metabolizers). 85% of patients reported improvement in chorea symptoms.

Conclusions: Complex neurobehavioral symptoms of HD frequently require pharmacological interventions. Pharmacogenomics testing may help guide effective medication management.

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Exploring Outcomes of Long-term Physical ACtivity and Exercise Engagement in People with Huntington's Disease (PACE-HD): Evaluating Study Design and Intervention Processes

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Background: Mounting evidence suggests a role for physical activity in improving function and quality of life in people with Huntington's Disease (HD). We previously conducted a 12-month randomized controlled trial of a therapist-mediated long-term physical activity intervention (PACE-HD).
Objective: We report results from the embedded process evaluation to understand contextual factors surrounding the implementation of PACE-HD.
Methods: The intervention included therapist-led personalized coaching sessions that incorporated educational workbooks and activity monitors (Fitbits). Participants (n=22) completed questionnaires at 12 months focusing on factors affecting intervention delivery. Questions were rated on a Likert scale with some free-text responses. Answers to Likert scale questions were summarized using descriptive statistics. Free text was thematically analyzed.
Results: The intervention was delivered with high fidelity incorporating components of collaborative regulation and self-determination theory. Fitbits were used to track activity but were not frequently used as a motivational tool. Participants were able to engage in independent exercise but benefited from frequent therapist support. Participant-therapist interaction emerged as a key factor promoting physical activity and routine adherence above use of an educational workbook and physical activity monitor use alone.
Conclusions: The individualized support of a physical therapist is crucial to maintaining engagement in physical activity interventions in HD and should be integrated into disease management from the earliest stages. Use of educational workbooks and physical activity monitors (e.g., Fitbits) are helpful adjuncts but should not replace the individualized support by therapists. Tailoring interventions to individual needs is critical to successful implementation.

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Characterisation of a Disease-related Phenotype in Human iPSC-derived Huntington's disease Model Cells

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Background: The development of therapies to treat neuronal indications is hampered because less than 10% of findings derived from animal models can be translated to humans. Patient-derived induced pluripotent stem cells (iPSCs) enable the generation of models that can recapitulate disease phenotypes. However, conventional iPSC differentiation protocols are often lengthy, inconsistent, and difficult to scale. The lack of genetically matched (isogenic) controls for patient-derived models complicates the investigation of disease phenotypes. bit.bio has developed a robust iPSC reprogramming method (opti-ox™) that overcomes these limitations and enables the generation of cell types and disease models.
Objective: To compare gene expression and electrophysiology of a human iPSC-derived Huntington's disease (HD) model with its isogenic wild-type control.
Methods: We used CRISPR/Cas9-mediated genetic engineering to introduce a 50 CAG expansion in the huntingtin (HTT) gene of ioGlutamatergic Neurons. Cells were characterised by RT-qPCR, immunocytochemistry, bulk RNA-sequencing and microelectrode array (MEA) analysis.

Results: Successful on-target integration of a 50 CAG repeat expansion was confirmed by PCR and NGS-amplicon sequencing. Differential expression of HD-relevant genes was observed. MEA analysis demonstrated a disease-related functional phenotype indicated by a decreased spontaneous activity and significant reduction in the number of network bursts compared to the isogenic control.
Conclusions: We combined opti-ox™ technology and gene engineering to generate a human iPSC-derived Huntington's disease model, ioGlutamatergic Neurons HTT 50CAG/WT™. The cells show a Huntington's disease-related phenotype and differential expression of HD-related genes, making them a relevant isogenic model for investigating Huntington's disease.

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Olfactory Dysfunction is Associated with Severity of Cognitive and Motor Symptoms in Huntington's Disease

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Background: Although olfactory dysfunction has been reported in Huntington's disease (HD), the relationship between olfactory changes and the severity of HD clinical symptomatology is yet to be studied.
Objective: To evaluate olfactory dysfunction in HD gene expansion carriers (HDGECs) and to determine if olfactory changes correlate with known clinical manifestations of HD.
Methods: Cross-sectional study including 41 HDGECs and 43 age- and sex-matched controls. Olfaction was assessed using the 12-item Brief Smell Identification Test (BSIT). Participants completed a comprehensive clinical assessment that included motor (UHDRS®-TMS), cognitive (MoCA, SDMT, Stroop Test, and Social Perception-Affect Naming), behavioral (PBA-s), and functional capacity (UHDRS®-TFC) tests.
Results: HDGECs present a significant impairment in odor detection, as demonstrated by lower scores in the BSIT compared to controls. HDGECs also performed significantly worse than controls in all cognitive tests. Among HDGECs, better scores in the BSIT were associated with better scores in the motor and cognitive scales ($p<0.01$): UHDRS®-TMS ($r_s = -0.574$), MoCA ($r_s = 0.538$), SDMT ($r_s = 0.610$), Stroop Interference ($r_s = 0.502$), Social Perception ($r_s = 0.413$), and UHDRS®-TFC ($r_s = 0.569$). The same correlations were not significant among controls. In addition, olfaction was not associated with the score in the PBA-s.
Conclusions: HDGECs present with olfactory impairment, and worse olfactory function is associated with worse motor and cognitive symptoms in HD. Our findings suggest that olfactory changes can indicate the severity and progression of HD.

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Study Companion Input is Important for Total Functional Capacity and the Problem Behaviors Assessments

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Background: Underreporting of symptoms and denial of disease progression in Huntington's disease (HD) may impede symptom management and impact clinical trial data. The full impact of study companion (SC) input on functional measures and behavioral assessments has not been studied.
Objective: To determine if SC input influences the Total Functional Capacity (TFC) scale and the Problem Behaviors Assessment short form (PBA-s).
Methods: Two groups of US-based early manifest participants from Enroll-HD dataset were analyzed: presenting with a SC (defined as spouse/partner, parent, sibling, child, or other relative) (n=1431) or without a SC (defined as "no informant" in PBA-s) (n=1129). Participants were matched for age, sex, and education. Baseline data were compared using an independent samples t-test and Pearson correlation coefficient.
Results: TFC was higher in the group without a SC (mean±SD) (11.0±1.9 vs. 10.1±2.1, $p < 0.0001$). The group without a SC reported lower scores on executive function (1.8±4.0 vs. 3.3±4.9, $p < 0.0001$), irritability/aggression (2.2±3.8 vs. 3.4±5.0, $p < 0.0001$), and apathy domains (1.7±3.1 vs. 2.3±3.7, $p < 0.0001$). Depression and psychosis domain scores did not significantly differ between groups.

Conclusions: Corroborated data supported by SCs are critical for obtaining accurate functional and behavioral scale assessments. Even in early manifest studies, SC input should be strongly encouraged or mandated. Exploration of responses across cultures and over time deserves further study.

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Real-World Effectiveness of Deutetrabenazine (DTBZ) in Patients with Huntington Disease (HD)-Associated Chorea Who Previously Discontinued Tetrabenazine (TBZ) Because of Ineffectiveness

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Background: Real-world evidence on DTBZ for the treatment of HD-associated chorea in patients with prior TBZ use may help guide care.
Objective: To describe real-world effectiveness of DTBZ for HD-associated chorea in patients who previously discontinued TBZ because of ineffectiveness.
Methods: This retrospective chart review from an HD-specialty clinic included patients with a diagnosis of HD-associated chorea, DTBZ initiation between April 2017–December 2021, ≥2 documented clinical encounters, and ≥3 months of chorea-related care records post-DTBZ initiation. Last Unified Huntington's Disease Rating Scale–Total Maximal Chorea (TMC) scores before DTBZ initiation and after last stable dose were analyzed for patients who previously discontinued TBZ because of ineffectiveness and had TMC scores available.
Results: Of 80 patients included in this chart review, 7 previously discontinued TBZ because of ineffectiveness and had TMC scores available. Among these patients, mean TMC score decreased by 3.7 (SD, 5.2) over study follow-up. Among patients who switched to DTBZ after a treatment gap (n=3), scores decreased for all patients (mean decrease, 7.3 [SD, 2.1]), and among patients with an overnight switch from TBZ to DTBZ (n=4), scores decreased for 2 patients, increased for 1, and did not change for 1 (mean decrease, 1.0 [5.3]). The observed safety profile in the full study population was consistent with the known DTBZ safety profile.
Conclusions: In this real-world study, in a limited (n=7) subset of patients with a known history of discontinuing TBZ because of ineffectiveness, TMC scores mostly improved with DTBZ treatment.
Abstract Summary: Real-world effectiveness of deutetrabenazine (DTBZ) for the treatment of chorea associated with Huntington Disease (HD) was evaluated in a retrospective chart review based on Unified Huntington's Disease Rating Scale–Total Maximal Chorea (TMC) scores. Here, we focused on the subgroup of patients who previously discontinued tetrabenazine (TBZ) because of ineffectiveness. TMC scores improved with DTBZ treatment in patients with a known history of discontinuing TBZ because of ineffectiveness.
Conflict of Interest and Material or Resource Support: This study was supported by funding from Teva Branded Pharmaceutical Products R&D, Inc. Victor Sung has been a consultant for Teva Pharmaceuticals and Roche Genentech and holds a leadership role in the Huntington's Disease Society of America. Ashley White does not have any conflicts of interest to disclose. Hela Romdhani, Sakshi Sethi, and Debbie Goldschmidt are employees of Analysis Group, which has received payments from Teva Pharmaceuticals in relation to this study. Nayla Chaijale, Ayelet Yaari, Mark Forrest Gordon, Amy Yang, and Rinat Ribalov are employees and/or shareholders of Teva Pharmaceuticals.

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Treatment Patterns, Effectiveness, and Satisfaction with Deutetrabenazine in Huntington Disease When Initiated Using a 4-Week Patient Titration Kit: Interim Results of the START Study

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Background: Deutetrabenazine is a vesicular monoamine transporter type 2 inhibitor for treatment of adults with tardive dyskinesia (TD) and Huntington disease (HD)-associated chorea (1). A 4-week patient titration kit was launched in July 2021 to assist patients in titrating to optimal deutetrabenazine dosages.
Objective: To evaluate the real-world treatment patterns, effectiveness, and satisfaction with deutetrabenazine, initiated using the titration kit.
Methods: START is an ongoing, 2-cohort (TD and HD) study evaluating the real-world usage of deutetrabenazine treatment when initiated using the titration kit. Results from the 17 patients enrolled in the HD cohort are presented in this interim analysis.
Results: 71% (12/17) of patients successfully completed the titration kit (completed within 5 weeks or reached optimal dose [≥24 mg/day] within 4 weeks). Mean (SE) deutetrabenazine dosages were 26.8 (1.99) mg/day at week 12, and 92% (12/13) of patients reaching week 12 had a maintenance dosage ≥24 mg/day. Mean (SE) adherence with the kit was 91% (5.5%). 50% (8/16) of patients achieved treatment success ("much"/"very much" improved) at week 12 per Clinical Global Impression of Change (GIC); 63% (10/16) per Patient GIC. Mean Total Maximal Chorea scores decreased by 4.4 (41%) from baseline to week 12. All 12 (100%) of the patients who completed the satisfaction questionnaire found it easy to use the kit.
Conclusions: The 4-week patient titration kit enabled patients to titrate to optimal deutetrabenazine dosages with high satisfaction, adherence rates, and effectiveness similar to the pivotal clinical trials.
Abstract Summary: START is an ongoing, routine-care, prospective, single-arm, 2-cohort (tardive dyskinesia and Huntington disease [HD]) study evaluating dosing patterns, effectiveness, and satisfaction with deutetrabenazine, initiated using a 4-week patient titration kit. As of this interim analysis, 71% of patients with HD-associated chorea successfully completed the kit, with a mean (SE) dosage of 26.8 (1.99) mg/day at week 12. 50% of patients achieved treatment success and 100% of responding patients found it easy to use the kit.

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Vesicular Monoamine Transporter Type 2 (VMAT2) Inhibitors for the Treatment of Chorea Associated with Huntington Disease: Survey of Number Needed to Treat and Number Needed to Harm

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Background: Number needed to treat (NNT) and number needed to harm (NNH) estimates can be used to better understand the frequencies of certain outcomes in clinical practice. Lower NNTs and higher NNHs are associated with positive treatment profiles.
Objective: Calculate NNTs and NNHs for vesicular monoamine transporter type 2 (VMAT2) inhibitors deutetrabenazine, valbenazine, and tetrabenazine in the treatment of Huntington disease (HD)–associated chorea.
Methods: NNTs for treatment success ("much" or "very much" improved on the Clinical Global Impression of Change [CGIC] or Patient GIC [PGIC] at week 12) and NNHs for individual adverse events were calculated using publicly available data from registration trial information for deutetrabenazine, valbenazine, and tetrabenazine. No comparison across these studies can be made or is intended.
Results: For deutetrabenazine, NNTs (95% CIs) for CGIC and PGIC treatment successes were 4 (3-9) each; NNH (95% CIs) was significant for diarrhea (12 [6-175]). For valbenazine, NNTs for CGIC and PGIC treatment successes were 4 (3-9) and 5 (3-17); NNHs were significant for somnolence (9 [5-40]), urticaria (11 [7-45]), and rash (13 [7-81]). For tetrabenazine, NNT for CGIC treatment success was 3 (2-5; no PGIC data available); the 4 lowest significant NNHs (of 7 total) were for somnolence (4 [3-8]), insomnia (5 [4-9]), and depression and akathisia (6 [4-13] each).
Conclusions: VMAT2 inhibitors have demonstrated both efficacy and safety for treatment of HD-associated chorea. Evaluating NNT and NNH can help clinicians evaluate potential positive and negative effects of different interventions.
Abstract Summary: Number needed to treat (NNT) and number needed to harm (NNH) estimates were calculated for the vesicular monoamine transporter type 2 (VMAT2) inhibitors deutetrabenazine, tetrabenazine, and valbenazine in the treatment of chorea associated with Huntington disease (HD). NNTs for treatment success, defined as "much" or "very much" improved on the Clinical Global Impression of Change (CGIC) or Patient GIC (PGIC) at week 12, ranged from 3-4 and 4-5, respectively, for the 3 VMAT2 inhibitors. Significant NNHs were diarrhea for deutetrabenazine and somnolence, urticaria, and rash for valbenazine; the 4 lowest NNHs for tetrabenazine were for somnolence, insomnia, depression, and akathisia. These estimates support the demonstrated efficacy and safety of VMAT2 inhibitors for the treatment of chorea in HD.
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Indirect Treatment Comparison of Valbenazine with Deutetrabenazine for Improvement in Total Maximal Chorea Score in Huntington Disease

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Background: The efficacy of vesicular monoamine transporter 2 inhibitors on chorea associated with Huntington disease (HD) has been demonstrated in randomized Phase 3 trials of valbenazine (KINECT®™-HD) and deutetrabenazine (First-HD).
Objective: To conduct an indirect treatment comparison (ITC) between valbenazine and deutetrabenazine using data from KINECT®-HD (N=125) and First-HD (N=90).
Methods: For valbenazine and placebo, mean change and 95% CI values for Unified Huntington's Disease Rating Scale® Total Maximal Chorea (TMC) score were obtained from the pivotal trial publication. For deutetrabenazine and placebo, TMC values were digitally estimated from the figure in the pivotal trial publication. Mean change for drug versus placebo was estimated using the inverse-variance method. An ITC of valbenazine versus deutetrabenazine was conducted using the Bucher method at 2, 4,6 weeks and at maintenance (KINECT®-HD: average of Wk10/Wk12; First-HD: average of Wk9/Wk12).
Results: The ITC of TMC score improvement significantly favored valbenazine over deutetrabenazine at Wk2 and Wk4, with relative treatment effects for valbenazine versus deutetrabenazine of 1.87 (95% CI: -3.23, -0.52; p<0.05) and -1.84 (95% CI: -3.43, -0.25; p<0.05), respectively. At Wk6 and maintenance, the difference of valbenazine versus deutetrabenazine demonstrated similar treatment effects of -0.84 (95% CI: -2.45, 0.78; p=NS) and -0.77 (95% CI: -2.42, 0.87; p=NS), respectively.
Conclusions: In this ITC of valbenazine and deutetrabenazine, valbenazine improved chorea as early as Wk2 (at the initial 40 mg dose), with a similar therapeutic effect to deutetrabenazine during maintenance. Subsequent ITC analyses will focus on additional study outcomes, including safety.

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A Minimal Clinically Important Difference for UHDRS® Total Maximal Chorea Score as a Measure of Chorea Severity in Huntington Disease

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Background: In KINECT®-HD (NCT04102579), a Phase 3 trial of valbenazine for chorea associated with Huntington disease (HD), valbenazine significantly reduced chorea severity versus placebo as assessed by UHDRS® Total Maximal Chorea (TMC) score (prespecified primary endpoint). Currently, no minimal clinically important difference (MCID) has been established for TMC score.
Objective: To establish an MCID for TMC score using KINECT®-HD data.
Methods: Anchor-based analyses were performed to identify MCID thresholds for TMC score (range, 0 to 28). MCID was defined as the mean (±SEM) within-subject TMC score change corresponding to an exactly 1-point improvement in Clinical Global Impression of Severity (CGI-S: range, 1=normal/not at all ill to 7=extremely ill) or Patient Global Impression of Severity (PGI-S: range, 1=none to 5=very severe). MCID analyses included all assessment data regardless of treatment.
Results: Based on 34 participants with a 1-point reduction in CGI-S, the MCID for TMC was -4.0 (±0.6). Based on 22 participants with a 1-point reduction in PGI-S, the MCID for TMC was -4.3 (±0.8). Per these anchor-based results, the least-squares mean change of -4.6 for valbenazine on the primary endpoint exceeded the MCID. Moreover, 57% of valbenazine-treated participants had a ≥4-point reduction in TMC score versus 20% of placebo-treated participants.
Conclusions: Data from KINECT®-HD suggest that changes in TMC score of -4.0 (CGI-S anchor) or -4.3 (PGI-S anchor) correspond to minimal clinically meaningful improvements in patients with HD-related chorea. Valbenazine exceeded these MCID thresholds in the primary endpoint, and substantially more valbenazine-treated participants had a ≥4-point reduction in TMC.

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Sustained Improvements with Once-Daily Valbenazine in Chorea Associated with Huntington Disease: Interim Results from a Long-Term Open-Label Study

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Background: In KINECT®-HD (NCT04102579), valbenazine significantly improved chorea versus placebo in adults with Huntington disease (HD). KINECT®-HD2 (NCT04400331) is an ongoing open-label study evaluating the maintenance of valbenazine's effect on chorea and long-term safety in adults with HD, including KINECT®-HD study completers.
Objective: To present pre-planned interim analyses from KINECT®-HD2.
Methods: Participants receive once-daily valbenazine (starting dose: 40mg; target maintenance dose: 80mg) for up to 156 weeks. Efficacy outcomes include mean changes from baseline in the Unified Huntington's Disease Rating Scale® Total Maximal Chorea (TMC) score and response status ("much improved" or better) for Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C). Efficacy outcomes up to Wk50 are reported. Treatment-emergent adverse events (TEAEs) are presented for participants who took ≥1 dose of study drug. Interim outcomes were analyzed descriptively.
Results: Of 127 participants at time of analysis, 98 were from KINECT®-HD. Mean TMC score reductions were observed by Wk2 with valbenazine 40mg (-3.4 [±3.1], n=118) and sustained with ≤80mg from Wk8 (5.6 [±3.6], n=110) to Wk50 (-5.8 [±4.1], n=66). At Wk50, 76.9% (50/65) of participants were CGI-C responders and 74.2% (49/66) were PGI-C responders. Among 125 participants receiving treatment, 119 (95.2%) reported ≥1 TEAE; 17 (13.6%) discontinued due to a TEAE. The most common TEAEs were falls (30.4%), fatigue (24.0%), and somnolence (24.0%).
Conclusions: Interim data from the open-label KINECT®-HD2 study indicated that long-term treatment with once-daily valbenazine was well tolerated and provided clinically meaningful improvement in chorea severity for up to ~1 year.

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A Wearable Movement Sensor Substudy of KINECT®-HD, a Phase 3 Trial of Valbenazine for the Treatment of Chorea Associated with Huntington Disease

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Background: In KINECT®-HD, greater chorea improvement was found with once-daily valbenazine versus placebo in adults with Huntington disease (HD). This was also the first Phase 3 trial to include a wearable movement sensors substudy.
Objective: To assess wearable sensor-derived changes in movement, posture, gait, and chorea among HD trial participants.
Methods: Passive collection of movement data between study visits was performed using the BioStamp nPoint® system. Participants wore three sensors (chest and anterior thighs) for two 7-day periods (±2 days) during the screening period (baseline) and following the Week 10 visit (maintenance). Changes from baseline to maintenance in physiological measures, including truncal chorea and gait asymmetry measures, were analyzed using paired t-tests within each treatment group. Sensor-related adverse events (AEs) were analyzed descriptively.

Results: Among 38 KINECT®-HD participants who entered the substudy, 27 were included for analysis (valbenazine=12, placebo=15) based on available data and adherence (wore sensors for ≥5 hrs/day for ≥5 days during baseline and maintenance). Significant improvements from baseline to maintenance were found for truncal chorea and gait asymmetry measures in the valbenazine group (all $p<0.05$) but not the placebo group. Six participants reported any sensor-related AE, all mild; one AE (skin irritation) resulted in sensor removal.
Conclusions: Consistent with KINECT®-HD results, truncal chorea improved with valbenazine in this substudy; gait asymmetry measures also showed improvement. These results support further exploration of how digital measures can be used to detect meaningful symptom changes in individuals with HD to improve clinical research and care.

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The Huntington Disease Health Index (HD-HI): Measuring Changes in Disease Burden in Response to Valbenazine During the KINECT®-HD Trial

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Background: The Huntington Disease Health Index (HD-HI) is a validated, patient-reported outcome designed to evaluate Huntington disease (HD)-related burden. It comprises 13 subscales that measure distinct areas of symptomatic burden and a total score (range: 0=no burden to 100=highest burden).
Objective: To describe HD-HI results from KINECT®-HD (NCT04102579), a 12-week Phase 3 trial of valbenazine versus placebo for HD chorea.
Methods: Mean changes of HD-HI total and subscale scores from baseline to Wk10 and Wk12 were analyzed descriptively (prespecified exploratory study endpoints). A post hoc ANCOVA analysis of change from baseline (CFB) to Wk12 was performed to explore potential treatment effects.
Results: In the prespecified analysis of mean CFB at Wk12, numerical improvements were greater with valbenazine than placebo in 8 of 13 HD-HI subscales (mobility, abnormal movements, hand/arm function, emotional health, social performance, social satisfaction, cognition, gastrointestinal health/swallowing function) and total score; no meaningful change was found with valbenazine in domains assessing fatigue or daytime sleepiness. In the post hoc analysis, the HD-HI subscales with the largest least-squares mean differences (LSMDs) between treatment groups were abnormal movements, emotional health, hand/arm function, cognition, and social satisfaction. There was statistically significant improvement with valbenazine versus placebo for abnormal movements (LSMD: -6.7 [-12.9 to -0.4]; P=0.0379).
Conclusions: In addition to HD-HI improvements observed in subscales related to motor function that support the efficacy of valbenazine on the impact of chorea, this analysis of HD-HI data suggests potential favorable effects in other important HD-related domains, notably emotional health, cognition, and social satisfaction.

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Predictive Testing for Huntington Disease in Canada: Pilot Survey

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Background: Predictive genetic testing for Huntington disease (HD) has been available in Canada since gene discovery in 1983, initially consisting of multiple in-person visits. Over time, protocols have become modified, in part due to the COVID-19 restrictions.
Objective: To review the current process for predictive testing in five centers: Calgary, Edmonton, Ottawa, Toronto, and Vancouver.
Methods: Information was obtained from genetic counsellors (GCs) or geneticists from the five centers.
Results: In all five centers, predictive testing occurs through Departments of Medical Genetics, organized by GCs, who have a major role in counseling. Edmonton and Vancouver have a total of four virtual visits (two counselling, results session, follow-up call). Calgary has five visits: four in person and one follow-up by phone. Ottawa has three virtual visits (counselling, results, follow-up). Toronto has five virtual or in person visits (three counselling, results, follow-up). In most centers, a geneticist sees the patient in at least one of the sessions. In Calgary, a session with a psychiatrist is routine while only arranged if needed in the other four centres.
Conclusions: In Canada, predictive testing for HD is offered to at-risk adults by specialized teams of GCs, geneticists, and psychiatrists, although number and type of visits vary among centers. Differences in patient outcomes and satisfaction is unknown. HD testing process remains more involved than for some other neurogenetic disorders and further research is planned to determine optimum number and types of visits.

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Influencing Huntington's Disease Monitoring with Remote Collection and Quantification of Blood-based Biomarkers

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Background: Remote assessment of biomarkers could increase uptake in research for populations with more barriers against them attending in-person visits. For example, healthy far-from-onset Huntington's disease (HD) mutation carriers have larger childcare burden, still work full-time, and may not attend HD specialist services as they do not have symptoms yet. Home-testing could also allow for frequent sampling that could enrich our understanding of the natural fluctuations of these biomarkers.
Objective: We aimed to develop a self-sampling blood collection method and validate it for remote quantification of HD blood biomarkers.
Methods: Blood samples were collected from controls and HD mutation carriers using a novel finger-prick blood collection method and standard venepuncture. Neurofilament light (NfL), GFAP and Total Tau were quantified using Simoa technology. Total protein was quantified using BCA Protein assay. Haemoglobin was quantified using ELISA. Pearson's correlation, linear regression and intra-class correlation (ICC) were used to compare methods.
Results: Blood collection method (venepuncture or finger-prick) and processed sample type (plasma or serum) did not impact NfL concentrations ($r>0.96$, $R^2>0.93$, $ICC>0.99$, $p<0.0001$). GFAP was also correlated across methods unlike total Tau. NfL in both plasma and serum from capillary and venous blood was stable after 3-day delay ($r>0.92$, $R^2>0.84$, $ICC>0.92$, $p<0.0001$) and 7-day delay in processing ($r>0.91$, $R^2>0.88$, $ICC>0.94$, $p<0.0001$). Haemoglobin increased with processing delay length.
Conclusions: These results suggest that this novel collection method is suitable for remote monitoring of Neurofilament light protein in HD mutation carriers.

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Stand Up and JOIN-HD! The Juvenile Onset Initiative for Huntington's Disease

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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 launched in Q1 2022. As of August 2023, there are 81 families pre-registered. Participants are invited to self-enrol 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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Comparison of Self Versus Proxy Reporting in FuRST 2.0 as an Indicator of Impaired Insight

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Background: The Functional Rating Scale 2.0 (FuRST 2.0) is a self-reported 24-item questionnaire developed to measure functional impairment in people with Huntington's disease (pwHD). However, impaired insight, a known feature in HD, may interfere with self-reporting. The degree of under-reporting symptoms due to impaired insight and the impact of disease progression is not clear. To address this, we evaluated the discrepancies between self and proxy reporting of functional ability in FuRST 2.0.
Objective: Determine whether discrepancies exist between self and proxy reporting in FuRST 2.0 and assess impact of disease progression.
Methods: A cognitive debriefing study of FuRST 2.0 scale development involved separate interviews of 33 pwHD (17 male; age: M=48, SD=14; CAG: M=43, SD=3) and their companions (14 male; age: M=50, SD=14). The degree of discrepancy on the FuRST 2.0 scores was defined as the number of items where caregivers rated higher impairment than pwHD. Association between disease progression and discrepancy was evaluated.
Results: The median discrepancy on 22 items was 6 points (range 0, 20). Disease progression impacted the degree of discrepancy: higher discrepancy was observed with more advanced stages according to the HD Integrated Staging System [HD-ISS]. Worse scores on SDMT (r=-0.54), Stroop (r=-0.67), TMS (r=0.67), and TFC (r=-0.47) were associated with greater discrepancy.
Conclusions: Accurate self-reporting may be impaired in pwHD in advanced stages. Further studies in larger cohorts may delineate the extent and domains of under reporting. Limits of reliability of FuRST 2.0 related to disease progression in advanced HD may need to be defined.

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Understanding the Needs of Young People Impacted by HD

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Background: HDYO is an international non-profit organization providing support, information and resources to young people impacted by HD. There is limited research focused on understanding global needs of young people impacted by HD. HDYO launched a series of surveys to improve understanding of these needs. These surveys explore the

resources used, community perspectives/experiences with HD research, and challenges accessing resources.
Objective: We present data from our first survey, exploring resource utilization and unmet needs of young people impacted by HD.
Method: Participants provided informed consent prior to completing an anonymous, online questionnaire. This study has ethics board approval.
Results: Between March and June 2023, 106 eligible people responded to the survey. Seventy-six (75%) identified as female, 91% were white. Most respondents (62%) were between 18 and 35 with the remaining 38% aged 36+ years. Thirty-eight respondents were HD positive, eight gene-negative, and 29 were gene-unknown.

The most frequent information sought was research updates (n=75), personal stories (n=51), HD related medical information (n=49), and mental health support (n=44). Social media was the most frequently endorsed medium to access information (n=69), followed by HD association websites (n=62), and HDBuzz (n=50). For HDYO specific resources, respondents frequently endorsed HDYO website (n=42), followed by social media (n=37), virtual (n=30), and in-person events (n=27). Responders not using HDYO resources cited preferences for local supports (n=11) or lack of utility (n=12).
Conclusions: Results of this survey will directly inform resources provided by HDYO and are relevant to HD associations supporting this community.

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Update on U.S. Phase I/II Clinical Trial of AMT-130 Gene Therapy for the Treatment of Huntington's Disease

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Background: AMT-130 is an investigational, AAV5 viral vector containing an exon-1 HTT-targeting miRNA, thereby lowering total-HTT mRNA.
Objective: Describe interim 12 and 24-month results from high- and low-dose cohort participants, respectively (NCT04120493).
Methods: Trial design, including inclusion and exclusion criteria, has been previously reported.
Results: 26 patients, 10 low-dose (6 treated, 4 control) in cohort-1 and 16 high-dose (10 treated, 6 control) in cohort-2 are included. Baseline means (range) for low-dose were: age 49.5 (44-57), CAG repeat length 42.2 (41-44), CAP score 417.7 (322.9-485.9), TFC 12.0 (11-13), TMS 14.5 (8-23), and cUHDRS® 14.7 (11.5-18.28). For high-dose, these were: age 47.8 (33-65), CAG repeat length 41.8 (40-46), CAP score 380.2 (278.9-495.0), TFC 11.9 (9-13), TMS 13.9 (6-26), and cUHDRS® 13.9 (6-26). Most common adverse events (AEs) for treated cohorts were related to the surgical procedure: procedural headaches, complications, and pain. Two serious AEs since resolved, severe headache and CNS inflammation, occurred in high-dose. Compared to baseline, clinical function was generally preserved at 24 and 12-months for low-dose and high-dose, respectively. As expected, CSF-NfL transiently increased non-dose dependently in all treated

participants, peaking approximately 1-month post-surgery before decreasing below and approaching baseline for low-dose and high-dose, respectively.

The mHTT data showed some reduction in treated cohorts, in an overall variable data set. Reduction was more pronounced in low-dose than high-dose. Total whole brain volume did not reduce significantly in treated cohorts compared to control.

Conclusions: AMT-130 was generally well-tolerated across both cohorts with a manageable safety profile and encouraging trends in clinical and biomarker outcomes.

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Recruiting for the KINECT®-HD Study: How the Huntington Study Group® (HSG®) and HSG® Credentialed Study Sites Collaborated with Sponsor for Successful Enrollment and Participant Engagement

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Background: KINECT®-HD™ (NCT04102579) was a randomized, double-blind, placebo-controlled clinical trial that assessed safety and efficacy of valbenazine for chorea in patients with Huntington disease (HD). In total, the trial screened 167 participants and enrolled 128 participants into the eight-month protocol. The HSG® credentialed sites and HSG® worked collaboratively with Neurocrine Biosciences, Inc., using their shared expertise to understand the unique requirements and challenges of effectively enrolling HD patients into KINECT®-HD™.

Objectives: We assessed the reported recruitment sources in comparison with the anticipated recruitment plan to understand the impact of each method. The results of this assessment will provide insight into recruitment and enrollment of HD patients in future studies.

Methods: KINECT®-HD used multiple recruitment methods, including collaboration with HD organizations, social media campaigns, presentations at HD meetings, and empowerment of trial sites to recruit within their patient populations.

Results: This assessment presents the association of different recruitment methods on enrollment. The majority of participants (n=154) were recruited through local HSG® study site populations, while the remaining participants (n=13) were recruited through word of mouth, neurologist referrals, and through participating study site recruitment websites.

Conclusions: This assessment highlights the importance of utilizing HSG®'s expertise and resources, community connections, and established relationships for clinical trial recruitment. The results of this assessment will influence allocation of recruitment resources for future studies. HSG® sites collaborating with the HSG®, and study Sponsor can effectively share resources and knowledge to minimize recruitment duration, screen failures, and subject attrition in future HD studies.

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The Huntington's Disease Network of Australia (HDNA): Preparing for the Advent of New Therapies for Huntington's Disease

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Background: Clinical trials worldwide are testing treatments for Huntington's disease (HD). In Australia, preparations are essential to prepare for rapid deployment of new treatments. The HDNA, funded by the Australian National Health and Medical Research Council, is scaling up preparation for clinical trial participation and the advent of new treatments.

Objective: To lay the essential groundwork in Australia for disease modifying therapies for HD.

Methods: 1) We created a patient self-enroll HD registry for all people affected by HD (diagnosed, at risk, family members, carers) to map their locations, obstacles in accessing HD clinical care, community services, and their experiences with Commonwealth-supported disability insurance entitlements. 2) A prevalence study is in progress. 3) We are formalizing an Australian HD clinical trial network. 4) We are developing a culturally-tailored HD project, facilitating inclusivity and diversity.
Results: We will summarize the findings from the first 200+ participants in the registry and describe the clinical sites and patient populations currently known across Australia.
Conclusions: Like Australia, many countries are reflecting on their preparedness for the advent of new, life-changing therapies for HD. By sharing our approaches and resources, together we can accelerate the realization of new therapies for people with HD.

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The GUIDE-HD Study: A Randomized Controlled Feasibility Trial Comparing Guided Self-Help for Anxiety among Huntington's Disease Gene Expansion Carriers Compared to Treatment as Usual

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Background: Psychological interventions for people affected by Huntington's disease are in their infancy. People with HD commonly experience anxiety and, within the general population, a significant evidence base exists for talking therapies such as guided self-help. GUIDE-HD is based on cognitive behavioural and acceptance and commitment therapy, designed to meet the specific needs of an HD population. The intervention has been developed in collaboration with people affected by HD, and involves 10 sessions with a facilitator and accompanying workbooks. Three caregiver sessions are also offered to supplement learning and skills-development.
Objective: The overall aim of is to assess the feasibility of a randomised clinical trial (RCT) evaluating the clinical effectiveness of a psychological intervention, compared to usual care, in reducing anxiety in individuals with pre-manifest and early-stage HD.
Methods: The study compares guided self-help with treatment as usual. Fifteen HD gene expansion carriers will be randomly allocated to each group. Participants are currently being recruited across the UK. Using both quantitative and qualitative methods, data will be analysed to assess whether the current intervention and study design meets pre-determined criteria that would indicate feasibility to progress to a larger RCT.
The trial has been pre-registered: https://www.isrctn.com/ISRCTN47330596
Results: The study is currently ongoing, and results will be published following the trial completion towards the end of 2024.
Conclusions: Given the current paucity of evidenced psychological interventions for people with the expanded Huntington's gene, GUIDE-HD will assess the feasibility of progressing this current intervention to a full trial.

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Staff Experiences and the Perceived Impact of Team Formulation Sessions in a Specialist Huntington's Disease Inpatient Unit

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Background: Research exploring psychologically informed perspectives of distress for people with Huntington's disease (HD) is limited. To address this, Dale and colleagues developed a clinical formulation model and tool for understanding distress among people with HD, based on a biopsychosocial framework. The authors suggest that it can be used to supplement and structure team formulation sessions for staff working with people with HD. Studies within other areas of healthcare indicate such sessions can help improve team working, intervention planning, and in understanding service-user needs and behaviour. To date, this approach has not been evaluated within the context of HD services.

Objective: To explore staff experiences of attending team formulation sessions on a specialist HD inpatient unit in the UK and how staff perceive the sessions have impacted upon the service and their practice.
Methods: Using a purposive sample, semi-structured one-to-one interviews will be undertaken to gather data from different members of the multidisciplinary team who have attended at least one team formulation session. Data will be analysed using framework analysis.
Results: Data gathering is currently ongoing; the results will be published following completion of the service evaluation towards spring 2024.
Conclusions: This service evaluation will explore the practical application of Dale et al's clinical formulation tool, designed to help understand distress among people with HD. Exploring staff experiences of attending team formulation sessions using this HD-specific model, will allow us to evaluate the strengths and weaknesses of this approach and to inform the structure and direction of future sessions.

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Co-design of a Physical Activity Volunteer Training e-kitbag for Huntington's Disease with Stakeholders (PAVOT-HD)

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Background: Physical activity buddies within and external to the Huntington's Disease (HD) community who support each other to be active could positively impact physical activity engagement, social interaction, raise awareness and reduce stigma.
Objective: To co-design, create, and evaluate a digital training resource for physical activity buddies to support people with HD to be physically active in their local communities.
Method: A co-design workshop was held with people gene positive for, or who have early-stage HD, the HD Association of England and Wales (HDA) and digital technology experts (June 2022). The content and resource were created and evaluated by people from the HD community, Disability Sport Wales, and HDA.
Results: Stakeholders identified a need for the resource to be "fun" and "interactive" to support engagement and sustained use. Based on findings of the co-design workshop, the digital resource comprises stories from the personal perspectives of people with HD to include "hints and tips" about supporting someone with HD to be active (podcasts, filmed video clips), written information, and links to other existing resources about HD. It is accessible on a smart phone/tablet/PC. Following evaluation, further content was added to raise awareness of and address common misconceptions of HD that stakeholders had experienced. The resource is being refined for dissemination (August 2023).
Conclusions: Once finalised the resource will be incorporated into HDA resources, Disability Sport Wales Inclusive training for volunteers, and into an "Active MotiMates" mobile application for which the prototype has been created.

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Participant and Site Satisfaction of Televisits in Development of the Virtual Unified Huntington's Disease Rating Scale (vUHDRS®)

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Background: The COVID-19 pandemic brought an increased need for remote assessments. While the Unified Huntington's Disease Rating Scale is the standard assessment for Huntington's Disease (HD), a virtual version has not been studied. There is evidence for patient satisfaction of a hybrid televisit/

in-person clinical model for chronic neurological disorders; however, information is needed on patient/site satisfaction for televisits in HD.
Objective: To assess the satisfaction of study participants and research sites participating in an observational study involving vUHDRS® assessments.
Methods: Individuals with motor manifest HD consented to four visits over four weeks. Visits included in-person and televisits. Participants used either personal or study-provided technology. Participant and site surveys evaluated satisfaction with the televisit and administration of remote assessments.
Results: Sixty participants with HD from 16 U.S. sites were enrolled. Overall, participants and sites were either satisfied or very satisfied with the televisit (95% of participants and 85% of site staff, respectively), the technical connection quality (98% and 83%, respectively), and the comfort of televisits (95% and 85%, respectively). Participants and sites either agreed or strongly agreed that they would be interested in using televisits for future research (73% of participants and 82% of site staff, respectively).
Conclusions: Satisfaction with televisits was lower for sites than participants, but both were favorable. The majority of both groups were interested in future trials involving televisits. This study suggests that using the vUHDRS® measure would be an acceptable supplement to visits, while also demonstrating technology was not a significant barrier for participants or research sites.

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Mutant huntingtin Drives Development of a Functionally Advantageous Brain Early in Life, Followed by Prolonged Worsening of Skills

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Background: Studies propose abnormal neurodevelopment's role in Huntington's disease (HD) etiology. While most studies suggest that mutant HTT (mHTT) leads to early developmental aberration, another theory posits that it drives functionally advantageous brain development, vulnerable to rapid degeneration. Age-based functional mapping studies have yielded early insights into the advantage hypothesis. However, years-to-onset (YTO) based examination, which provides a robust approach by accounting for both age and CAG length, is lacking.
Objective: To explore brain function trajectories in relation to YTO in premanifest HD.
Methods: Cognitive, motor, and behavioral data from preHD Gene-Expanded (GE) and Gene Non-Expanded (GNE) children and young adults (6-25 years) in the Kids-HD study were examined. These measures were statistically modeled to assess YTO-based changes.
Results: GE participants showed higher cognitive scores versus GNE participants far from onset (between 50 and 28 YTO). Beginning around 40 YTO, a cognitive decline was observed, resulting in GE participants scoring lower than GNE participants at approximately 18 YTO, and this downward trend continued. While this pattern of early advantage and continuous decline was also observed for depression/anxiety and aggression/opposition (modified by a sex effect) measures in GE versus GNE participants, hyperactivity/inattention and motor function measures did not show an early advantage but exhibited a steadily worsening decline.
Conclusions: mHTT may drive the development of a striatal circuit that subserves superior early-life function, followed by prolonged decline. These findings support the notion that mHTT may have been positively selected for human brain evolution and posits a unique pathoetiology for degeneration.

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Contrasting Associations of Apathy and Depression with Loss of Functional Capacity in HD

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Background: It can be difficult to disentangle depression versus pure apathy syndrome and their relationship to Huntington's Disease (HD) progression. Apathy can be either a pure syndrome or a prominent feature of Major Depression.

Objective: We assessed the joint relationship to loss of functional capacity of the apathy and depression scales used in Enroll-HD.
Methods: Using both the Total Functional Capacity (TFC) and the combined UHDRS® (cUHDRS®) scores as outcomes, we modeled the joint relationship of the Problem Behaviors Assessment (PBA) Depression and Apathy scores, as well as the subscores of the Hospital Anxiety and Depression (HADS) scale. We examined the ISS Stage III group of Enroll-HD. (Approximately 17,600 visits from 7,390 participants.)
Results: Higher PBA Apathy and HADS Depression were strongly associated with lower functional capacity. In contrast, worse PBA Depression and HADS Anxiety were associated with higher function.
Conclusions: The contrasting functional capacity associations of PBA Apathy and Depression illustrate the specificity to HD of apathy in the absence of low mood. The PBA Depression rating is focused on low mood and sadness. In the general population, depression and anxiety frequently co-occur, and their similar associations with higher function in this study reinforce the above interpretation, as pure apathy may inhibit sadness and anxiety. In contrast, the HADS Depression items focus on the apathy symptoms of depression and do not directly address low mood. Therefore, the HADS Depression scale may reflect an undifferentiated mix of depression and apathy—an ambiguity partially clarified by simultaneous consideration of PBA Depression.

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Predicting Early HD Progression Using Motor Diagnosis, the Prognostic Index, and ISS Staging

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Background: Progression rates shortly before and after motor diagnosis of Huntington's Disease (HD) are predicted by the HD Prognostic Index (PIN) score and the clinical determination of motor diagnosis. The recently introduced Integrated Staging System (ISS) will likely play an important role in future HD clinical trial design. Its role as an additional progression predictor has not been widely studied.
Objective: Describe the joint roles of motor diagnosis, PIN score, and ISS staging in predicting HD progression rates before ISS Stage 3.
Methods: Using Enroll-HD, we modeled longitudinal progression rates of candidate clinical outcome measures based on combinations of ISS stage, PIN range, and motor diagnosis (UHDRS® Diagnostic Confidence Interval 4).
Results: These three measures were substantial interacting predictors of HD clinical progression over 4 years. ISS Stage 2 is a heterogenous group with progression strongly predicted by diagnostic status and PIN score.
Conclusion: Among those in ISS Stage 2, rates of functional decline are substantially faster in those also given a motor diagnosis. These rates are similar to those in Stage 3 with TFC scores between 10 and 12. Among those without a motor diagnosis, the distinction between Stage 2 versus Stages 1 or 0 adds additional prognostic value beyond the PIN. However, the PIN score remains a strong predictor of progression regardless of ISS Stage, and about half of those with relatively elevated PIN scores are classified below Stage 2. Those in Stage 2 with low PIN scores have little risk of imminent progression.

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A Metabolomic Comparison of Participants with Fast or Absent Functional Progression from 2CARE, a Randomized, Double-Blind Clinical Trial in Huntington's Disease

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Background: Huntington's Disease (HD) is increasingly recognized for diverse pathology outside of the nervous system. To describe the systemic biology of HD in relation to functional progression, we previously analyzed the plasma and CSF metabolome in a cross-sectional study of HD participants with varying functional impairment. Increases in plasma arginine, citrulline, and glycine, with decreases in total and D-serine, cholesterol esters,

diacylglycerides, triacylglycerides, phosphatidylcholines, phosphatidylethanolamines, and sphingomyelins were observed.
Objective: We further explored whether prior observations could be substantiated by looking longitudinally in pooled plasma from individuals over three years, and whether differences exist between those with faster or slower clinical progression.
Methods: We analyzed plasma from participants receiving placebo in 2CARE, a 5-year, randomized, double-blind HD clinical trial.
Results: More metabolites were different in the fast progression group than those who did not progress (111 vs 20, nominal $p<0.05$). All changes with faster progression were decreases, while some increased in absent progression. Many of the metabolites that decreased in the fast group had higher concentrations at Screening than the absent group, but ended up being lower for absent progressors by Year 3. Changes suggesting greater oxidative stress and inflammation (kynurenine, diacylglycerides, cysteine), disturbances in nitric oxide and urea metabolism (arginine, citrulline, ornithine, GABR), lower polyamines (putrescine and spermine), elevated glucose, and deficient AMPK signaling correlated to faster progression.
Conclusions: Metabolomic differences between fast and absent progressors suggest the possibility of predicting functional decline in HD, and possibly delaying it with interventions to augment arginine, polyamines, and glucose regulation.

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Cortical Control of Gait and Balance During Single and Dual Tasks in Huntington's Disease: An fNIRS Imaging Study

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Background: Individuals with Huntington's disease (HD) have difficulty multitasking, so that previously automatic tasks like ambulation may require more attentional resources to maintain stability and prevent falls. There is limited understanding of neural mechanisms underlying cognitive-motor relationships in HD. fNIRS provides a noninvasive means to functionally image the brain to understand the neural underpinnings of impaired gait and balance in HD.
Objective: To examine the cortical control of gait and balance in HD under single-task (ST) and dual-task (DT) conditions.
Methods: Eighteen HD and 20 age-matched control participants completed ST/ DT gait and balance testing with concurrent prefrontal (PFC) and posterior parietal (PPC) cortical activity monitoring by fNIRS. The cognitive DT for balance was a verbal fluency task during 30 sec trials and that for gait was the Digit Vigilance task during one minute, 10-meter walk tests.
Results: Individuals with HD had greater PFC and PPC activation during ST walking vs. controls but no difference in the DT condition. They had significantly lower PPC activity during a DT balance condition compared to controls. Unlike controls, there were no differences in PFC or PPC activation across balance conditions in HD, despite significantly worsening postural sway during DT.
Conclusions: More PFC attentional resources appear to be necessary in HD during ST but not DT gait. Together with reduced PPC activation in HD during a DT balance task, suggests that individuals with HD reached a recruitment ceiling at low difficulty levels which they were not able to recruit beyond with increasing task difficulty.

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Harmonizing Remote and Onsite UHDRS® Motor Assessment Using Machine Learning

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Background: COVID-19 impacted clinical research and healthcare delivery worldwide. Though many clinical assessments could be obtained via remote

devices (iPads) and video research visits, a complete motor exam was not possible.
Objective: The purpose of this research was to use machine learning models to address missing data from remote UHDRS® total motor ratings.
Methods: Predict-HD and Enroll-HD datasets were preprocessed to ensure data quality and compatibility. Five machine learning models were employed to predict the missing UHDRS® motor components: Decision Tree; Random Forest; Extra Trees; Gradient Boosting; Multi-layer Perceptron. Models were trained using a 10-fold cross-validation approach. Evaluation metrics were applied to quantify the model's ability to predict the missing components based on data with complete motor exams. Multiple methods were applied to assess the importance of each acquired feature in the prediction model. The top model was compared with in-person motor assessment scores using hold-out dataset applications.
Results: The Random Forest model displayed superior accuracy (mean=0.892), precision (0.885), recall (0.89), F1 score (0.887), and lower mean squared error (4.12) compared with all other models.
Conclusions: Accurate prediction of missing UHDRS® motor components is critical in monitoring HD progression and treatment responses. A significant advantage of using machine learning for remote UHDRS® assessments is its potential for cost-saving and logistical simplification. The methods here can reduce burden on participants, researchers, and facilities while increasing participant visit frequencies and engagement, and improving study efficiency. Optimizing remote assessment and machine learning will improve remote capture of clinical change in HD over time.

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Huntington's Disease In-Home Caregiver Education Program

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Background: Individuals with mid-late stage Huntington's Disease (HD) may require an in-home aide or placement in a long-term care facility. HD education and awareness needs to be provided to those managing HD care as there is a high turnover rate of paid caregivers. Paid caregivers may have limited knowledge about HD.
Objective: (1) To create a training and support program for paid in-home HD caregivers. (2) To create a training manual based on the information provided in the training program and insight from program participants to be distributed to the HD community.
Methods: This pilot program will recruit 10 paid in-home caregivers. All patients receiving care at home will be over age 60. The program curriculum will be a comprehensive guide to caring for individuals with HD in the home. The program will consist of a pre-test, three virtual educational sessions, one in-person educational session, and a post-test. All participants will be compensated for their time and provided with transportation to/from the one in-person session. They will also receive a printed copy of training materials.
Results: HD-CERC will utilize results from the pre-test and post-test to measure program effectiveness. HD-CERC will use feedback from participants in the development of the in-home training manual.
Conclusions: This program will improve the quality of care for individuals with HD, reduce burden on HD families, and provide support to paid in-home aides. Some materials developed in this program may prove useful for caregiving in other dementia populations.

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Reliability of the Virtual Unified Huntington's Disease Rating Scale (vUHDRS®)

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Background: The Unified Huntington's Disease Rating Scale (UHDRS®) is the gold-standard measure to assess Huntington's disease (HD) related

motor, cognitive, behavioral, and functional changes, but has been only assessed for in-person use. Out of necessity, components of the UHDRS® were used remotely during the Covid-19 pandemic.
Objective: To determine the reliability of administering all sections of the UHDRS® virtually compared to in-person.
Methods: Participants with motor manifest HD were recruited for a one-month observational study. Cognitive, behavioral, and functional scales were assessed at an in-person visit, televisit, and second in-person visit. A complete motor examination was conducted in person, and feasible items were assessed virtually. Approximately half of participants were provided standardized technology and half used personal equipment. Reliability of the vUHDRS® components was assessed using Intraclass correlation Coefficients (ICC), separately by equipment type.
Results: Sixty participants (31 personal equipment, 29 study-provided equipment) were recruited from 16 sites. The ICC for the modified motor scores of the televisit vs. second in-person were 0.93 for personal and 0.95 for provided equipment. For Total Functional Capacity, ICC were 0.94 and 0.93, respectively. All measures of cognition, behavior, and other functional scales had ICC consistent with excellent reliability. As a quality check, the intra-rater reliability of the total motor score between the two in-person visits was high (ICC=0.92 and 0.93, respectively).
Conclusions: Remote administration of all sections of the UHDRS® had excellent reliability, using personal or study-provided equipment. The virtual version of this scale can reliably be used for clinical and research assessments.

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Establishment of the Huntington Study Group® Social Work Working Group

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Background: Social work is critical to the interdisciplinary care of Huntington's Disease (HD) families. There are many unmet needs in HD care which social workers are uniquely trained to address, including access, financial stressors, emotional challenges, advance care planning, and caregiver burden. Increasingly, social workers are also contributing to HD research, yet didn't have a niche within the Huntington Study Group® (HSG®) working groups. The HSG® is a global leader in HD clinical research and HSG® working groups bring together subject matter experts in various fields.
Objective: To organize a group of social work subject matter experts as an official working group under the HSG®.
Methods: At the 2022 HSG® annual meeting, a small group of social workers discussed forming a working group, including the purpose, goals, and rationale for the new group. Later discussions developed these ideas and recruited additional experts.
Results: The HSG® formally approved the Social Work Working Group in May of 2023.
Conclusions: This working group provides a platform for social workers to contribute to HD research and minimize gaps in HD care. Future projects under development include best practices in HD social work, assessment of HD social worker satisfaction, and research questions social workers are well poised to answer, including access, caregiver needs, trauma, apathy, and more.

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Impact of Age and Cognition on Duration of Televisit during the HSG® vUHDRS® Study

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Background: Huntington's Disease (HD) causes motor and cognitive impairment. This, along with age and less familiarity with technology, may impact the duration of remote research visits (televisit). With the increasing use of televisits, determining potential limitations is critical for developing remote study assessments.

Objective: To assess whether age, cognitive scores, or Total Motor Score impact the duration of televisits.
Methods: Sixty individuals with motor manifest HD participated in a US-based study examining the reliability of a modified version of the UHDRS® during a televisit. Chi-square and T-tests compared participants' baseline age, cognitive status, Total Motor Score, and equipment type used (personal or study-provided) by site report of televisit time lasting >60 minutes vs. ≤60 minutes.
Results: Sites reported that the televisit took >60 minutes for 29 participants and ≤60 minutes for 30 participants. The >60 minutes group was older (mean ± SD) (59.8 ± 13.4 vs 51.0 ± 9.5 years, p=0.005) and had lower Symbol Digit Modalities Test scores (23.7 ± 9.4 vs 29.3 ± 13.7, p=0.07) than the ≤60 minutes group. The two groups did not differ significantly on Stroop Word Reading scores, Total Motor Scores, or between the use of personal vs study-provided equipment.
Conclusions: Individuals who took longer to complete televisits were older and had lower cognitive scores. These participants may need more guidance and support to optimize the efficiency of televisits.

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A Brain Penetrant Small Molecule Induces Preferential Degradation of Mutant but Not Wild Type huntingtin Protein via Selective Autophagy

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Background: In Huntington's Disease (HD), mutant huntingtin protein (mHTT) is the principal cause of pathological changes including HTT protein aggregation and compromised protein degradation, transcription, and synaptic function. An easily administered agent that treats the entire body and selectively targets toxic mHTT, leaving sufficient normal HTT function to support healthy physiology, could provide significant clinical benefit by restoring cellular balance.
Objective: To identify mHTT-selective small molecule protein degraders with potential to be HD therapeutics.
Results: Employing a high content/high throughput screen, we identified multiple chemical scaffolds that prevent mHTT aggregation and lower mHTT protein without affecting HTT mRNA levels. To further characterize these compounds, we studied HD and unaffected donor fibroblasts and demonstrated a Q-length-dependent inhibition of autophagy. One compound, ORI-113, overcame this autophagy deficit in HD fibroblasts by enhancing selective autophagy. Additionally, ORI-113 preferentially reduced mHTT protein, while sparing normal HTT protein in HD fibroblasts. In iPSC-derived HD neurons, ORI-113 reduced mHTT protein, prevented HD pathologies detected with high content imaging and normalized both transcription and protein expression profiles. Furthermore, ORI-113 was well distributed in plasma, brain, and muscle of mice. Treatment of YAC128 mice with ORI-113 for two weeks resulted in significant reduction of mHTT in cortex and striatum with no adverse effects observed, suggesting that ORI-113 may have therapeutic potential. Several analogues of ORI-113 demonstrated improved potency and favorable properties. Origami Therapeutics is selecting compounds for further preclinical studies.
Conclusions: ORI-113 and its analogues represent potential therapeutics for HD with a novel mechanism of action.

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A Randomised Controlled Trial, of N-Acetyl Cysteine (NAC), for Premanifest *Huntingtin* Gene Expansion Carriers (NAC-preHD)

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Background: N-Acetyl Cysteine (NAC) delayed onset of motor abnormalities, enhanced survival, and slowed striatal atrophy in Huntington Disease (HD) mouse models. NAC improved mitochondrial function and ameliorated glutamatergic dysfunction.
Objective: NAC-preHD aims to test the hypothesis that oral NAC is effective in slowing caudate atrophy and delaying motor onset of HD, when compared to placebo, in an enriched population of premanifest *Huntingtin* gene expansion carriers.
Methods: NAC-preHD is a Phase II, multi-site Randomised Placebo-Controlled Trial, with allocation concealment, triple-blinding (participant, outcome assessment and statistical analysis), and analysis by Intention-to-Treat. NAC-preHD will recruit 160 *Huntingtin* gene expansion carriers, expected to develop clinical HD within 10 years of enrolment, as predicted by the Langbehn formula. Participants will be randomly allocated to 1g twice a day of oral NAC or Placebo over 3 years, in a 1:1 ratio. Primary outcome measures will be caudate atrophy rate on volumetric MRI, and rate of motor phenoconversion, at three years. Secondary and exploratory outcome measures include changes in cognition, changes in mood and behavioural symptoms, daily function, quality of life measures, and safety and tolerability of NAC. NAC-preHD has an 80% power to detect a 16% (half a standard deviation) reduction in caudate atrophy rate, and has an 81% power to detect a 65% reduction in motor phenoconversion rate at 3 years.
Results: We will present the biological underpinning and rationale for trial design for NAC-preHD. Ethical approval: Western Sydney Local Health District Human Research Ethics Committee (2021/ETH12013). ClinicalTrials.Gov registration number: NCT05509153.

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Cross-sectional Interhemispheric Connectivity Changes in Huntington's Disease

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Background: The white matter is severely affected in Huntington's disease (HD) and may contribute significantly to clinical manifestation. In particular, the corpus callosum, which contains interhemispheric networks of fibers, has been shown to degenerate in HD. We have developed a novel analytical tool to evaluate the corpus callosum that takes advantage of directional tract density patterns (dTDPs) to objectively and automatically quantify white matter integrity. We hypothesized that the integrity of the CC was reduced not only in symptomatic but also in pre-symptomatic individuals, with relative sparing of specific segments of the CC.
Objective: To evaluate inter-hemispheric connectivity in HD.
Methods: We scanned a cohort of Pre-HD (N=40, age=45.8±11.3), HD (N=46, age=51.4±12.1) and 46 healthy controls (HC) on Siemens 3T MRI scanner at the A. A. Martinos Center for Biomedical Imaging. We used diffusion and T1 weighted images to evaluate interhemispheric connectivity to study, as reported previously (Demir and Rosas, 2023) to obtain the directional tract density patterns (dTDP) for each CC region. Individual dTDPs were used to create group plots depicting the median dTDP of the group with the shaded area filling the gap between the upper and lower quartile dTDPs. Statistical analysis was performed along each direction in polar space using a paired t-test.
Results: There was a significantly reduced dTDP in all regions of the CC in the HD as compared to the HC ($P<0.05$), with a trend in the PHD group.
Conclusions: There are significant changes in interhemispheric connectivity in HD that may contribute to clinical symptoms.

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Novel Eye Movement Markers in Huntington's Disease

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Background: Identifying effective biomarkers is of particular importance to Huntington's Disease (HD)

with disease modifying treatment therapies under investigation and ongoing clinical trials around the globe. Eye movements (EM), currently used as a biomarker for conditions including concussion and schizophrenia, may be an effective biomarker in HD as well. Basal ganglia, brainstem nuclei, and the vestibular system are organized to produce different EM. The complexities of vision, requiring the integration of multiple cortical and sub-cortical areas, are vulnerable to the neurodegenerative process of HD. Importantly, in addition to having established characteristics in the healthy adult population, the effects of pharmaceuticals and intoxicants on EM have been well documented. EM can be measured quickly, accurately, and non-invasively using eye trackers and can be compared directly to previously established metrics.

Objective: The purpose of this study was to confirm previous findings of vertical and horizontal saccades and anti-saccades, as well as to provide clarity to findings related to OKN in individuals with HD at different stages of disease using a comprehensive EM battery and highly reliable eye tracking instrumentation. In addition, we aimed to determine if there is/are particular EM that would be best suited to serve as biomarkers in HD.

Methods: Eighteen participants with a genetically confirmed diagnosis of HD were compared to eight healthy non-HD peers. Eye movements were recorded binocularly at 1000 Hz. All participants undertook testing of prosaccades, antisaccades, smooth pursuit (two subtests for each; i.e., horizontal and vertical), as well as OKN (four subtests; up, down, left, and rightward drift). Finally, a one-minute sample of self-paced saccades was also recorded in 17 participants with HD and seven non-HD peers.

Results: Preliminary results showed no significant differences between those with HD and non-HD peers in OKN or the dynamic parameters of prosaccadic eye movements. As expected, there was a significant increase in antisaccade errors in HD participants (Control = 24%, HD = 48%; $p<0.001$). The self-paced saccade test revealed significantly fewer saccades greater than 5deg as compared to the control participants (x Control = 140, x HD = 88; $p<0.001$).

Conclusions: While only preliminary results are presented here, they demonstrate a novel rapid and sensitive indicator of disease in HD. While some previous studies have reported decreased velocity and amplitude of saccades, we have shown that individuals with HD also make significantly fewer true self-paced saccadic movements, potentially decreasing the availability of environmental information to be utilized during functional movements.

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Prodromal Changes in Cognitive Domains as a Prognostic Indicator of Forthcoming Huntington Disease Severity: Lesson from Enroll-HD

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Background: Huntington disease (HD) cognitive changes precede motor manifestations. The Enroll-HD platform includes four cognitive measures of information processing speed (IPS). We are eager to seek clinical markers in the life stage that are as close as possible to the age of onset (i.e., the so-called prodromal HD phase) because this is the best time for therapeutic interventions.

Objectives: Our study aimed to test whether cognitive scores in prodromal Enroll-HD mutation carriers show potentiality to predict the severity of motor and behavioural changes once HD became fully manifest.

Methods: From the global Enroll-HD cohort of 21.343 participants, we firstly selected a premanifest Cohort #1 (i.e., subjects with Total Motor Score (TMS) < 10 and Diagnostic Confidence Level (DCL) <4, N=1.222). From this cohort, we focused on a prodromal Cohort #2 of subjects who were ascertained to phenoconvert into manifest HD at follow-up visits (i.e., subjects from 6<TMS>9 and DCL<4 to TMS≥10 and DCL=4, n=206).

Results: The main results of our study showed that low IPS before phenoconversion of Cohort #2 predicted the severity of motor and behavioral manifestations. By combining the four IPS cognitive

measures (e.g., Categorical Verbal Fluency Test; Stroop Color Reading Test; Stroop Word Reading; Symbol Digit Modalities Test), we generated a Composite Cognition Score (CCS). The lower the CSS score (<-1.5 standard Deviation of the mean), the higher were the TMS and the apathy scores in the same longitudinally followed-up patients, after phenoconversion.

Conclusions: CCS might represent a clinical instrument to predict the prognosis of mutation carriers who are close to manifest HD.

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Low Glucose Transporter Levels and Hypometabolic State before Brain Cortex Degeneration in Paediatric-Onset Huntington disease Children with Highly Expanded CAG Repeats

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Background: Paediatric Huntington disease with highly expanded mutations (HE-PHD; >80 CAG repeats) presents atypically, compared to adult-onset Huntington disease (AOHD), with neurodevelopmental delay, epilepsy, abnormal brain glucose metabolism, early striatal damage, liver steatosis, and reduced lifespan.

Objective: Since genetic GLUT-1 deficiency syndrome shows a symptom spectrum similar to HE-PHD, we investigated the potential role of the two main glucose transporters, GLUT-1 and GLUT-3, in HE-PHD.

Methods: We compared GLUT-1 and GLUT-3 protein expression in HE-PHD (i.e. paediatric-onset with mutation size >80 CAG), juvenile-onset (JOHD, i.e., adult-onset <20-25 years) and AOHD brains (n=2; n=3; n=6) and peripheral fibroblasts (n=3; n=2; n=2) versus healthy controls (n=6; n=6). We also investigated mitochondrial complexes and hexokinase-II protein expression.

Results: GLUT-1 and GLUT-3 expression were significantly lower in HE-PHD frontal cortex (p=0·009; p=0·017) versus controls. In fibroblasts, GLUT-1 and GLUT-3 expression were lower compared to controls (p<0·0001; p=0-043). In the frontal cortex, this occurred without evidence of extensive neuronal degeneration. HE-PHD patients had deregulated mitochondrial complex expression, particularly complexes II-III, levels of which were lower in frontal cortex versus controls (p=0·027; p=0·002) and AOHD patients (p=0·052; p=0·002). Hexokinase-II expression was also lower in HE-PHD frontal cortex and striatum versus controls (p=0·010; p=0·045) and in frontal cortex versus AOHD patients (p=0·013). Expression JOHD levels were consistently different to those of HE-PHD but similar to those of AOHD.

Conclusions: Our data suggest a dysfunctional hypometabolic state occurring specifically in paediatric Huntington disease brains before cortical degeneration.

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A Longitudinal Examination of the Relationship Between Apathy in Individuals with Huntington's Disease & Caregiver Quality of Life Perceptions

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Background: Apathy is a common neuropsychiatric feature of Huntington's Disease (HD). The symptom also correlates with cognitive and motor markers of disease progression. However, limited information is available pertaining to the relationship between individuals' degree of apathy and their caregivers' QOL perceptions. Additionally, longitudinal examination of these variables has not occurred.
Objective: This study investigated longitudinal changes in the apathy scores of individuals with HD as well as their relationship with caregivers' QOL scores.
Methods: Data were collected from the initial manifest visit of Enroll-HD participants accompanied by a caregiver (n=2,201) and annually thereafter for a five-year period. Linear mixed effect models were utilized to investigate changes in apathy scores at each annual interval, controlling for HD participant's age, sex, CAG repeat, as well as a random effect. Similar models were constructed to evaluate changes in caregiver QOL scores. Next, differences in variables' scores at each annual visit relative to baseline values were calculated. Finally, an evaluation of the relationships between the changes in apathy and caregiver QOL scores was conducted.
Results: Mean annualized change in apathy was 0.27 points per year ($t=8.17$, $p<0.0001$). For caregiver QOL, mean annualized change was 0.15 points per year ($t=-8.68$, $p<0.0001$). Annualized change in patient apathy scores significantly predicted annualized change in caregiver QOL ($t=-7.22$, $p<0.0001$) across a five-year period.
Conclusions: As apathy in individuals with HD increased over time, caregiver QOL significantly decreased. Absence of initiative and emotional disengagement in individuals with HD may be key factors eroding caregivers' sense of well-being.

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A Pilot Study to Evaluate the Efficacy of Dextromethorphan/Quinidine (DM/Q) in Treating Irritability in Huntington's Disease

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Background: Irritability is one of HD's most common neuropsychiatric symptoms, often leading to aggressive behavior with severe consequences. No medications are approved to treat specifically irritability in HD, and the available treatments are off–label and imperfect. We hypothesize that dextromethorphan/quinidine (Nuedexta®) would decrease irritability in individuals with HD and minimize aggression and outbursts.
Objective: To prove the efficacy and safety of dextromethorphan/quinidine 20mg/10mg in patients with irritability due to HD.
Methods: Randomized, double-blind, placebo-controlled, crossover, proof of concept study with 20 adults with verified HD mutation and irritability [defined as an Irritability Scale (IS) score > 14]. Primary outcomes: improvement of irritability, described as a 4-point change from baseline in the IS. Secondary outcomes: irritability, as quantified by the changes in the total IS score; Change of behavioral symptoms (UHDRS®, HADS, PBA-s, NPI - Q); Change in the motor symptoms (TMS); Change in functional independence (TFC).
Results: Eighteen individuals completed the trial. Compared to baseline, we observed a significant reduction in the IS score with both placebo (mean decrease of 7.6 points, 27.5%) and dextromethorphan/quinidine (mean reduction of 8.8 points, or 32%) treatments. The results were similar when we analyzed the irritability/aggression score of the PBA-s. We did not find differences when comparing placebo and dextromethorphan/quinidine treatments. In addition, we did not find differences between treatments for any of the secondary outcomes.
Conclusions: Although we observed a pronounced decrease in the IS score after the treatment with dextromethorphan/quinidine, our study revealed a strong placebo effect, and there was no difference between treatments.

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CDKs Inhibitor Roscovitine Reduces Neuronal Toxicity of mHTT by Targeting HTT Phosphorylation at S1181 and S1201

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Background: Huntington's disease (HD) is a neurodegenerative disease caused by a single mutation in the huntingtin gene (*HTT*). The mutated HTT encodes a mutant protein (mHTT) with an expanded polyglutamine (poly Q), which preferentially affects human striatum. HTT is a large protein, with many posttranslational modification sites (PTMs). Previous studies indicated that PTM modifications altered mHTT toxicity both in cell and animal models of HD.
Objective: We aimed to find PTMs targeted by kinases, so that inhibitors can be used to reduce toxicity.
Methods: In vitro kinase assay was performed. Top hits kinase inhibitors were tested in HD cell models. Specific targets of inhibitor were evaluated in vitro. The in-vivo efficacy of selected kinase inhibitors was evaluated in mice.
Results: A total of 369 kinases were screened. Among those kinases, CDKs affected the phosphorylation of the serine of peptides that contain S1181-HTT and S1201-HTT. Knock-down of CDK5 but not CDK1 reduced mHTT cell toxicity. Overexpression of CDK5 increased cytotoxicity. Alterations of HTT S1181 and S1201 to alanine (A) had less toxic effect in our HD cell model, indicating that modifying S1181 and S1201 would reduce mHTT toxicity. A CDKs inhibitor, roscovitine, protected neurons from mHTT induced toxicity. Roscovitine reduced phosphorylation of S1181 and S1201 of mHTT through CDK5 but not CDK1. In vivo pharmacology indicated that roscovitine administration by IP penetrated the mouse brain. Subchronic administration reduced brain CDK5 activity.
Conclusions: Roscovitine reduced mHTT toxicity by targeting PTMs of mHTT. Inhibiting CDKs pathways is a potential therapeutic target to reduce mHTT toxicity.

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Q-Motor Measures Show Strong and Consistent Correlations with Core HD Clinical Endpoints across LEGATO-HD, PRIDE-HD, TRACK-HD and PROOF-HD

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Background: Q-Motor measures have been employed in multiple clinical trials in HD and beyond. They lack subjective errors, rater bias, and placebo responses and reveal more sensitivity to detect treatment effects and disease progression in manifest and premanifest HD than clinical scales.
Objective: To explore correlations and reproducibility between Q-Motor measures and clinical measures of global disability (cUHDRS®), global function (TFC), and motor dysfunction (UHDRS®-TMS) across different studies in HD.
Methods: The core Q-Motor tests "finger tapping" (digitomotography) and "pronate/supinate hand tapping" (dysdiadochomotography) were collected and analyzed at the baseline visits of the studies PRIDE-HD, LEGATO-HD, TRACK-HD and PROOF-HD across treatment groups. The primary Q-Motor tapping endpoint "Inter-Onset-Interval" (IOI) was extracted and correlated to the cUHDRS® [PROOF-HD/TRACK-HD], TFC, and UHDRS®-TMS and regressions were compared across studies.
Results: The analyses revealed robust correlations between the finger tapping IOI mean times and the cUHDRS® [r=-0.534 to -0.715], TFC [r=-0.347 to -0.507] and UHDRS®-TMS [r=-0.383 to 0.747] ($p<0.00001$ for all). Similar results were observed for the pronate/supinate hand tapping task and with IOI-SD (a measure of variability) and other tapping measures across tasks. Regression lines revealed similar and consistent slopes across the studies for all measures assessed.
Conclusions: Q-Motor assessments are highly correlated to clinical disability in HD as assessed by the cUHDRS®, TFC, and UHDRS®-TMS. This was observed across all Q-Motor measures assessed. The slopes of the regression lines were virtually identical

across the four independent studies suggesting a high reproducibility of the link between Q-Motor measures and disease severity and progression.

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Q-Motor Measures Show Consistent Improvements in Patients without Antidopaminergic Therapy Treated with Pridopidine 45 mg BID Compared to Placebo at Multiple Visits Up to 78 Weeks in PROOF-HD

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Background: Q-Motor measures provide sensitive, rater-independent endpoints assessing motor function in pre-manifest and manifest HD. Declines in Q-Motor measures correlate with measures of HD severity and progression such as cUHDRS®, TFC, UHDRS®-TMS, CAP-scores and brain-volume as demonstrated in TRACK-HD, PRIDE-HD, LEGATO-HD, AMARYLLIS and SIGNAL-HD studies.
Objective: To explore changes from baseline observed in Q-Motor measures between participants without antidopaminergic therapy treated with 45mg BID pridopidine versus placebo and their consistency at all visits employing Q-Motor assessments in the PROOF-HD study.
Methods: The core Q-Motor tests "finger tapping" (digitomotography) and "pronate/supinate hand tapping" (dysdiadochomotography) were collected and analyzed centrally and blinded at baseline, 26, 52, 65, 78 weeks. The primary Q-Motor tapping endpoint "Inter-Onset-Interval" (IOI) mean time and additional measures were extracted and changes from baseline between the groups were calculated at all visits using prespecified statistical models.
Results: Q-Motor finger tapping IOI mean times were significantly improved at all visits ($p<0.0001$ @ 26-weeks, $p=0.017$ @ 52-weeks, $p=0.013$ @ 65-weeks and $p=0.003$ @ 78-weeks) in the per-protocol population. Similar improvements were seen in other Q-Motor measures, e.g., Inter-Tap-Interval (ITI) mean time in pronate/supinate tapping also improved at all visits ($p<0.0001$ @ 26-weeks, $p=0.015$ @ 52-weeks, $p=0.013$ @ 65-weeks and $p=0.01$ @ 78-weeks). Changes were consistent across all visits. Q-Motor revealed no placebo-effects.
Conclusions: Q-Motor tapping measures reveal nominally significant and consistent improvements in patients without antidopaminergic therapy treated with pridopidine across all visits of the PROOF-HD study. These observations provide objective evidence for a beneficial effect of pridopidine in HD.

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Topline Results from the Phase 3 Trial of PRidopidine's Outcome on Function in Huntington's Disease (PROOF-HD)

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Background: Pridopidine is an orally available small molecule and potent sigma-1 receptor agonist that demonstrates neuroprotective effects in preclinical models of Huntington disease (HD).
Objective: Evaluate the efficacy and safety of pridopidine in a double-blind, placebo-controlled, Phase 3 trial.
Methods: PROOF-HD enrolled 499 adult-onset HD participants (TFC ≥7). The primary endpoint was mean change from baseline to week 65 in Total Functional Capacity (TFC). The key secondary endpoint was change from baseline in the composite UHDRS® (cUHDRS®), and additional endpoints included quantitative motor (Q-Motor), cognition (Stroop Word Reading (SWR)), and Quality of Life (HD-QoL). Prespecified analyses excluded participants on antidopaminergic medications (ADMs) (neuroleptics and anti-chorea medications) as their use may be associated with a worsening of disease progression in some patients.
Results: Pridopidine was well tolerated with safety comparable to placebo. The primary endpoint was not met. However, in prespecified analyses exclud-

ing participants on ADMs (n=99), pridopidine shows improvement from baseline in cUHDRS® at week 26, week 39 and week 52 and sustained benefit to week 78. Q-Motor and SWR are also improved from baseline at week 26 which is sustained out to week 78. A trend for improvement in Quality of Life is also seen in pridopidine participants excluding ADMs with improvement across many HD-QoL subdomains.

Conclusions: In pre-specified analyses excluding participants on ADMs, pridopidine significantly improved or stabilized all outcome measures for at least 1 year and was better than placebo up to week 78 for all endpoints.

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Clinical and Genetic Characteristics of Huntington's Disease in the Pakistani Population

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Background: Huntington's Disease (HD) is an autosomal dominant progressive neurodegenerative disorder characterized by motor, cognitive, and psychiatric abnormalities. Huntington's disease is caused by repeat expansion in the huntingtin (*HTT*) gene located on chromosome 4p16.3. HD is frequently reported in Western populations, but there is a scarcity of studies from Pakistan.

Objective: This study aims to analyze the clinical and genetic characteristics of HD in the Pakistani population.

Methods: HD patients along with their normal relatives and healthy controls from different regions of Pakistan were recruited. Patients were clinically evaluated, and brain MRI imaging was performed. Blood samples were collected for genomic DNA isolation. A PCR assay was established to analyze CAG repeat expansion in the *HTT* gene, and the number of repeats was confirmed by sequencing.

Results: Thirteen patients with HD phenotypes were evaluated. All patients have a familial history with 38.4% of paternal transmission. The age of onset of HD phenotype in 13 patients ranged from 20 to 49 years, except for a single patient who presented juvenile-onset HD. Clinical features observed in these patients included chorea, tremors, bradykinesia, dystonia, facial dysmorphism, progressive dementia, and low learning abilities. The average number of repeats in affected individuals was 55.1±14.9 (40 to 70) CAGs while 17.4 ±2.6 in normal healthy controls. A significant inverse correlation between the age of onset of HD and CAG repeats was observed.

Conclusions: This study represents the first molecular characterization of HD in Pakistani patients and defines the range of repeat expansion in the *HTT* gene within HD patients from Pakistan.

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Behavioral Manifestations of Patients with HD Compared to their Communities

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Background: Depression and anxiety in Huntington disease (HD) has a significant impact on quality of life for patients and families. Understanding the behavioral symptoms of HD, their progression, and potential contributing factors is both challenging and crucial to advance clinical care.

Objective: To further characterize the behavioral symptoms experienced by patients with premanifest HD (P-HD), manifest HD (HD), gene negative controls (GN, i.e.: blood-related relative without HD), and family controls (FC, i.e.: spouse of patient with HD).

Methods: Using a US-based cohort from Enroll-HD, the Problem Behaviors Assessment (PBA-s), and the Hospital Anxiety and Depression Scale/ Snaith Irritability Scale (HADS-SIS) were used to evaluate behavioral symptoms at the baseline visit in 727 participants (GN= 46, F = 101, PHD = 136, HD = 444). Unpaired t-tests and one-way ANOVA were employed.

Results: HADS-SIS revealed that FC were less depressed (3.48±6.03 (Mean ±SD), p= 0.041), irritable (1.28±2.72, p=0.0042), and apathetic (0.57±2.26, p= 0.043) than P-HD, whereas GN controls had no significant differences in depression, irritability, and apathy from P-HD. A one-way ANOVA between all groups revealed that 16 out of the 22 measured subcategories of PBA-S were statistically significant,

including severity of depression (F=6.98, p= 0.0001), irritability (F=7.47, p< 0.0001), and apathy (F=29.6, p< 0.00010).
Conclusions: Psychiatric manifestations in the US Enroll-HD cohort with P-HD are more similar to GN controls versus FC. This finding is consistent with a possible genetic component to the behavioral aspect of HD beyond the CAG expansion.

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The Beauty of the Neurologic Exam - Identifying Functional Movements in HD

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Background: Functional Neurological Disorders (FND) are defined as neurologic signs due to alterations of the brain networks rather than structural abnormalities of the brain. FND have many overlaps with Huntington's Disease (HD), such as intermittent hyperkinetic movements, atypical gait patterns, and speech abnormalities. The coexistence of FND and HD has not been studied thoroughly. We have previously described a case of astasia-abasia as a presentation of FND in a patient with HD.
Objectives: We describe a case of HD with a functional speech pattern and tremor.
Methods: Case report of a patient evaluated at the HDSA Center of Excellence at UTHealth, Houston.
Results: The patient was a 68-year-old female with genetically confirmed HD, anxiety, depression, and with new onset neurologic symptoms. Her exam revealed normal saccade initiation and velocity, finger tapping without an increase in tone. She had intermittent stuttering speech without dysarthria that was distractible, suggestible, and consistent with a functional speech pattern in addition to a postural tremor with variable amplitude and frequency, positive entrainment, distractibility, and suggestibility, consistent with FND.
Conclusions: Functional neurologic disorders are common; however, the frequency is unknown in individuals with HD. The patient's exam findings were consistent with a functional tremor and speech pattern, neither common in HD. While stressors are not required for an FND diagnosis, they are not uncommon in individuals at-risk for or living with HD. FND is potentially treatable and reversible; therefore, increased awareness of the occurrence of FND in HD is important for appropriate diagnosis and treatment.

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HD Genetics: Insights from One Year of Telegenetics Services for Huntington's Disease

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HD Genetics

Background: On 8/5/2022, HD Genetics began offering fully remote genetic counseling (GC) and testing options for those at-risk for Huntington's disease (HD) in the United States.
Objective: This presentation is intended to demonstrate insights gathered from HD Genetics' client intake questionnaire and GC records, and client satisfaction following GC.
Methods: HD Genetics' services begin with an online client intake questionnaire, proceed to full GC services over multiple appointments, and include an optional post-results survey. We provide frequencies of client intake questionnaire responses, appointment completion, test results, and metrics of client satisfaction from post-test surveys.
Results: As of 8/6/2023, 258 clients completed an intake questionnaire and consented to being included in research; of these, 202 (78%) completed an intake visit, and 156 (77%) of these completed pre-test GC. Of these, 107 (69%) ordered a test kit for HD, 96 (90%) of which submitted their kit and were provided results via post-test GC. Overall, 61% of clients who submitted an intake questionnaire underwent pre-test GC and 37% went on to receive their results. Although 63% of clients reported they were not aware of current clinical trials and observational trials available for the HD community, 58% indicated interest in participation. All clients who completed post-results surveys (N=34) rated they were "very likely" to recommend HD Genetics' GC services.
Conclusions: After one year of operation, HD Genetics continues to offer accessible and patient-centered GC and genetic testing for the HD community, as well as connection to resources and research.

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An Analysis on the Effects of Cigarette Smoking on the Motor Symptoms of Patients with Huntington's Disease

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Background: Multiple investigations suggest nicotine may: 1) suppress chorea in animal models and preliminary human study, and 2) elicit neuroprotective effects. Despite common smoking in Huntington's Disease, these potential effects have not been investigated extensively.
Objective: The purpose of our study was to observe if a correlation between smoking tobacco and reduced motor symptom burden and/or slowed motor disease progression exists for patients with HD.
Methods: We performed a retrospective observational study using data from Enroll-HD to observe the effects of smoking tobacco on parkinsonian motor features, chorea, and Total Motor Score (TMS). These variables were compared between smokers (n=363) and non-smokers (n=1,080) with HD at the earliest record of clinical motor diagnosis and smokers (n=74) and non-smokers (n=220) at a time between three and four years later. This allowed the effect of smoking on symptom burden and motor progression to be observed.
Results: We found that there was no association between smoking and reduced TMS. Smoking was associated with a 7.8% decrease in chorea score (P=4.54e-2) and a 15% average increase in parkinsonism score (P=3.27e-4). There were no interaction effects between smoking and time. Three to four years of HD progression was associated with a 43.4% average increase in chorea score (P=1.04e-15), a 38.6% increase in average parkinsonism score (P=1.42e-13), and a 44.9% average increase in TMS (P=2e-16).
Conclusions: Our findings indicated an association between smoking and less severe chorea and an association between smoking and more severe parkinsonism. There were no effects of smoking on TMS.

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Impaired Blood-brain Barrier Precedes Motor Dysfunction and Striatal Atrophy in the zQ175 Huntington's Disease Mouse Model

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Background: In Huntington's disease, multiple recent clinical trials which are targeted at manifest HD have failed. Because almost 50% of the striatal volume has been lost at the time of clinical onset, it would be preferable to begin treatment in the premanifest period before the massive loss of the striatum.
Objective: In this study, water-extraction-with-phase-contrast-arterial-spin-tagging (WEPCAST) MRI was used to assess BBB permeability to water in the zQ175 HD mouse model.
Methods: This technique measures the water extraction fraction (E) and permeability surface-area product (PS), which are the indices of global BBB permeability to water.
Results: Quantitative analysis of E and PS values in wild-type mice revealed E to be 59.9±3.2% and PS to be 260.9±18.9 ml/100g/min. In contrast, 5 months old zQ175 HD mice exhibited significantly higher E (69.7±2.4%, P=0.026) and PS (318.1±17.1 ml/100g/min, P=0.040), indicating increased BBB permeability to water in zQ175 HD mice, while no motor symptoms and striatal atrophy were evident at this age. Western blotting results indicated decreased levels of tight junction protein (Claudin-5, ~ 36% reduction; ZO-1, ~ 27% reduction) in the striatum of zQ175 HD mice.

Conclusions: Altogether, these results suggest that altered BBB permeability to water is an early event prior to motor deficient and striatal atrophy in HD mice, further validation of these results in other HD models and human HD will be important to determine whether WEPCAST MRI measure of BBB can serve as a noninvasive biomarker to monitoring disease progression and evaluate treatment efficacy in HD.

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Accelerated Change in Motor Function Decline over the Early Natural History of Huntington's Disease: An Investigation from the Enroll-HD Database

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Background: Motor function plays a crucial role in indexing the progression of Huntington's disease (HD), particularly in the early stages of the disease. Insight into the timing of the change in motor function can offer valuable information for comprehending the natural disease history of HD.
Objective: To investigate whether decline in motor function accelerates before clinical motor onset (CMO) and to examine its relationship with the CAG length.
Methods: The Enroll-HD database served as the primary data source. Longitudinal measures on the Total Motor Score were utilized to assess motor function, and the time of first reaching a score of 4 for the diagnostic confidence level was used as the timing of CMO. A change point model was constructed, with CMO as the anchor event. The assumption was made that a linear trend exists both before and after the change point. Bootstrap method was used to provide a confidence interval for model estimates.
Results: A total of 14,935 participants were included in the analysis regardless of their motor onset status. Change points, indicating accelerated motor function decline, were identified for each specific CAG length. Additionally, we report the rate of change before and after these change points. On average across all participants, this accelerated change occurred approximately two years before the motor onset, and its timing varied with the CAG length.
Conclusions: An accelerated decline in motor function prior to the CMO was identified. This valuable information can be utilized in clinical trials to identify the target population and optimize participant selection for intervention studies.

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What People Diagnosed with Huntington Disease Say in Their Own Words About What Bothers Them

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Background: Direct to participant online research tools may help patients, researchers, and therapeutic developers better understand the problems and symptoms troubling patients.
Objective: We assessed verbatim, patient-reported problems from adults who self-identified as having been diagnosed with Huntington Disease (HD) using the myHDstory® research platform https://huntingtonstudygroup.org/myhdstory/.
Methods: Data were collected online from consenting United States residents who self-identified as having an HD diagnosis in earlier stages of illness. Verbatim reports of participants' bothersome problems due to their HD were collected by keyboard or voice entry of using the HD Patient Report of Problems (HD-PROP), a semi-automated natural language processing tool, and analyzed by clinical and

experienced experts to classify problems and functional consequences into symptoms.
Results: HD-PROP verbatim reports were obtained from 416 participants. Participants were 63% male, 34.5±9.9 (mean ± SD) years old, 46.4% Caucasian, and 9.5 (±8.4) years since HD diagnosis. The most frequently reported symptoms were in the Psychiatric Domain, with Depression the most common symptom (23.2%), followed by the Cognition Domain, with Concentration-Attention, and Memory as the most common symptoms (17% each). Within the Motor Domains, the most commonly reported symptoms were: Chorea/Tremor/Restlessness (14.4%), and Slowness (10.3%).
Discussion: Online reporting in HD patients' own words can inform clinically meaningful problems and symptoms and provide real-world data for application to clinical care and therapeutic development. Longitudinal assessment will clarify the utility of this approach for interventional studies.

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Data-driven Evidence Reveals the Absence of the Prevalence of Early Developmental Aberration in Juvenile-Onset Huntington's Disease

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Background: The current neurodevelopmental hypothesis of Huntington's disease (HD) suggests that at extremely high CAG repeats, mutant HTT adversely affects brain development, leading to developmental delay. While several cases have demonstrated this effect, there is still limited data available to support the prevalence of early developmental aberration such as developmental delay in reaching milestones in children with juvenile-onset HD (JoHD).
Objective: To evaluate the prevalence of developmental delay in children with JoHD.
Methods: We performed a retrospective analysis on participants from the Kids-HD and Kids-JOHD study conducted by the Nopoulos Laboratory. We compared birth history surveys that were completed by parents or guardians of JoHD patients (n=34) and Gene Non-Expanded (GNE) controls (n=100). We used basic statistical tools to analyze four birth and development chart parameters including birth weight, birth complications, prematurity, and early childhood milestones (a measure of developmental delay).
Results: There was not a statistically significant difference in the number of premature births, birth complications, or early childhood developmental milestones. Additionally, there was no statistically significant difference observed between the female birth weights, male birth weights, or when considering both male and female birth weights collectively.
Conclusions: Based on our findings, there is no indication of a prevalence toward significant early developmental aberration in children with JoHD. These findings contribute to a better understanding of how mHTT influences development in children with extremely high CAG repeats.

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The Huntington Mutation Modulates the Frequency of Autoimmune Diseases

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Background: Immune hyperactivity due to the Huntington mutation has been reported.
Objective: Immune dysregulation in Huntington's disease (HD) might affect the frequency of autoimmune disorders (AID).
Methods: The Enroll-HD periodic dataset 5 for European participants was analyzed. Both univariate and multiple logistic and linear regression analyses (MLRA) with age, gender and some cases the CAG repeat number were performed.
Results: AID frequency in controls (N=2,477, 7%) and HD mutation carriers (HDMC, N=10,595, 6.6%) was not different (p=0.446). When categorized as connective tissues diseases (CTD), endocrine (endo), dermatological (derm), gastrointestinal (gastro) as well as other AID, their relative frequency was significantly different (Chi-square test, p=0.0375) with lower and higher frequency of endoAID and dermAID in HDMC, respectively. Upon

MLRA, the odds ratio for dermAID in HDMC was 0.82 (95%CI 0.69-0.98, p<0.05), for dermAID 1.20 (0.98-1.50, not significant). This was due to lower and higher frequencies of autoimmune thyreoiditis (odds ratio 0.7, 0.6-0.9, p<0.01) and psoriasis (odds ratio 1.4, 1.1-1.8, p<0.01) in HDMC, respectively. Upon MLRA, in HDMC increasing CAG repeats negatively associated with AID risk (odds ratio 0.7, 95%CI 0.6-0.8, p<0.0001). Low pathological CAG repeats (<42) were associated with an increased risk (odds ratio 1.3, 95%CI 1.0-1.5, p<0.05), which CAGs >41 exhibit a tendency for a decreased risk (0.9, 95%CI 0.7-1.0, not significant). This was due to CTDs, which were 1.7-fold more frequent at CAG<42 and 1.6-fold more frequent at CAG >41 compared to family controls.

Conclusions: Our findings suggest that the HD mutation differentially affects the frequency of AID.

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