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Abstracts

1

Understanding the Aggregation Potential of the Huntington Protein

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BACKGROUND: Mutations within exon 1 of the huntingtin (HTT) protein trigger aggregation and accumulation within the brain and the periphery, leading to cell death and ultimately, clinical manifestation of Huntington's disease. HTT contains over 3000 amino acids but the exon 1, the suspected protein segment for driving pathology, accounts for less than 3% of the total structure. While regions outside exon 1 may also undergo proteolysis to create toxic fragments, their role in the disease process is not well understood.
OBJECTIVE: We therefore set out to characterize the aggregation potential of non-exon 1 HTT fragments.
METHODS: We used *in silico* (Aggrescan, Amylpred2, Expasy PeptideCutter), *in vitro* (proteomics, Thioflavin-T fluorescence, transmission electron microscopy (TEM), dot blot) and human post-mortem tissue analyses (western blotting and TEM).
RESULTS: *In silico* analysis predicted 110 aggregation-prone regions (APR) within HTT, of which five aggregation-prone peptides (AgPP) were further synthesized for *in vitro* experiments. The tested AgPP formed fibrils and oligomers within minutes in solution. *In silico* digestion of HTT revealed that several proteases can cleave HTT and generate AgPP, with trypsin producing the highest number of AgPP. Additional *in vitro* experiments confirmed trypsin's ability to produce AgPP capable of forming fibrils and oligomers. Of great relevance, western blotting on brain tissue of late-stage HD patients showed elevated levels of trypsin when compared to age- and sex-matched control subjects.
CONCLUSIONS: These preliminary findings indicate that HTT segments outside of exon 1 can aggregate, pointing to their role in the pathological processes underlying Huntington's disease.

2

First-in-Man Clinical Pilot Study Showing the Safety and Tolerability of Intravenous Injection of ER2001 (a Self-Assembled HTT-Specific siRNA) in Patients with Early Manifest HD

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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

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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. The primary endpoints were incidence of adverse events and abnormal clinical laboratory results. Participants received totally 8 intravenous injections of ER2001 and the treatment period of 14 weeks were followed by an observation phase of 84 days after the last injection.
RESULTS: A total of 10 HD patients including 5 males and 5 females, aged between 27 and 51 years were enrolled in this study. Up to now, there were total of 27 adverse effects and none of AEs was related to ER2001. A significant reduction in plasma mHTT from baseline was detected in HD patients. The PK, PD, and clinical outcomes will be updated once available.
CONCLUSION: Intravenous injection of ER2001 is safe and feasible in patients with early manifest HD, thus warranting further evaluation in randomized clinical trials.

3

A Video-Based AI Assessment of Movement Disorder in HD Patients

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BACKGROUND: Huntington's disease (HD) is a rare chronic progressive neurodegenerative disease. Movement disorder is the characteristic symptoms of HD and assessment of movement disorder is of great significance for the care of HD. Currently, movement disorder is evaluated using a time-consuming clinical rating scale UHDRS®. It is an urgent need to develop a convenient and effective assessment for HD severity.
METHODS: Forty-eight HD patients and 48 healthy controls were enrolled in the present study. All participants were required to provide 6 1-minute videos showing individuals in three positions including seated, standing, and walking positions. Video reliability test was conducted on twenty-seven patients to evaluate the consistency of scores derived from videos taken at home and scores derived in the clinic visit. A 3D convolutional module based on channel-spatial attention was used to extract data features, which were followed by an excitation-based 3D residual convolution module for feature learning. A fully connected layer based on channel-spatial attention was used to complete feature compression and obtain video classification results.
RESULTS: The video analysis was highly consistent with in-person visit (r = 0.969, P <0.001). The video-based AI assessment achieved accuracy of 85% in distinguishing HD patients and Healthy controls.
CONCLUSIONS: Our video-based AI assessment can achieve high accuracy in distinguishing HD patients and Healthy controls. A further validation is needed in large, multiple center study.
KEYWORDS: Huntington's Disease; Diagnosis; video-based AI assessment

4

Enroll-HD 2.0: Updates to the Enroll-HD Observational Study

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BACKGROUND: Enroll-HD was designed as an observational, longitudinal study to describe the natural history of Huntington's disease (HD) and support further research. The study has generated a vast amount of data and bio-samples which have been used in multiple analyses that have facilitated understanding of HD progression and variability and aided in identification of novel drug targets.
AIMS: The amendment to the Enroll-HD protocol (referred to as "Enroll-HD 2.0") aims to update the study to better reflect current scientific needs and support the next generation of clinical trials and research.
METHODS: The development of the amendment included a coordinating/writing team and multiple consultations with stakeholders. The final documentation (i.e., protocol, manuals, and sub-study proto-

cols) are being professionally reviewed for consistency and clarity.

RESULTS: The stated objectives remain unchanged. The amended protocol changes the study's design to put greater focus on early HD and use the HD-ISS to guide recruitment. Key changes include:

- Participants will be assigned to one of several cohorts, which allows for assessments and procedures to be tailored to disease stage.
- Shift away from an unspecified broad recruitment approach towards targeting specific populations using the HD-ISS and aim for an overall size of ~25,000 active participants.
- Flexibility to collect additional bio-samples.
- Sub-studies (including imaging) will be available at some sites for some participants.

CONCLUSIONS: Updating Enroll-HD is essential in order to optimize the platform's ability to support clinical research. The amended protocol will be distributed at Enroll-HD Congress 2024. Site start-up activities are scheduled to begin in 2025.

KEYWORDS: Enroll-HD, Protocol, Clinical Trial, Observational, Natural History

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Enroll-HD Platform Support for Clinical Trials and Studies in Huntington's Disease

Enroll-HD Platform Team

CHDI Management, New York, USA

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 more than 150 clinical sites in 23 countries.

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 participant recruitment, and site staff training and certification via a clinical training portal.

Several CHDI clinical studies have utilised a nested study design, such that Enroll-HD participant data are part of the nested study's schedule of assessments. These nested studies, which include HD-Clarity, imageClarity, and Later Stage Assessments for HD, use the platform infrastructure for study execution (e.g. EDC, monitoring resources).

Enroll-HD study data can also be used as run-in data to supplement trial analyses or as a natural history comparator.

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. Site intelligence is further supported in-silico screening of the Enroll-HD study database 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, and the HD Global Site Investigator (GSID-HD) feasibility database.

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Enroll-HD Platform Biosample Resources

Enroll-HD Platform Team

CHDI Management, Inc., New York, USA

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 June 1, 2024, 31,824 participants had been recruited from 189 sites in 23 countries spanning Europe, North America, Latin America and Australasia. 21,630 of those participants are still current (i.e. no mortality/end form). In its capacity of clinical research platform, Enroll-HD provides high quality clinical data and biosamples to qualified researchers in the HD research community via the Enroll-HD platform website (https://enroll-hd.org/for-researchers/). Due to its longitudinal nature, more than 82,000 completed 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. A new collection of PAX gene RNA blood tubes has recently been initiated; these samples should become available for research by the end of the year. Non-renewable biosample resources require review and approval by the Enroll-HD Scientific Review Committee (SRC) before release

whereas renewable resources can be released without SRC review. All biosample distributions come with a material, shipping and handling fee and a biosamples use agreement must be signed before biosamples can be shipped.

Currently available biosample resources: 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, buccal swabs.

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Enroll-HD Platform and Other HD Data Resources

Enroll-HD Platform Team

CHDI Management, Inc., New York, USA

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 June 1, 2024, 31,824 participants had been recruited to the study from 189 sites in 23 countries spanning Europe, North America, Latin America, Australasia. A total of 21,630 participants are still currently enrolled (i.e., no mortality/end form). To accelerate therapeutic research and development, high-quality clinical data and biosamples from several studies are made available to qualified researchers in the HD research community via the Enroll-HD platform website (https://enroll-hd.org/for-researchers/). Periodic releases of the Enroll-HD study dataset, including approximately 80% of the variables collected, are made available every ~2 years; the latest periodic dataset (PDS) - PDS6 - was released in January 2023. Enroll-HD data not included in PDS releases due to identification risk inflation may be obtained through special request, subject to review and approval by the Enroll-HD Scientific Review Committee (SRC) (https://enroll-hd.org/for-researchers/access-data-biosamples/). Clinical datasets from several additional HD studies are also made available free of charge through the Enroll-HD website, including REGISTRY, HDClarity and TRACK-HD/ON. Brain imaging datasets (e.g., IMAGE-HD, PREDICT-HD, and TRACK-HD/ON) are also available, as well as datasets generated from biosamples (i.e., GWAS, RNAseq, MiSeq, methylation, and proteomics data) collected across HD studies. A large, final REGISTRY dataset (RDS) has been prepared in a format similar to the Enroll-HD PDS; this RDS can augment the Enroll-HD PDS and thereby increase the total number of participants for HD disease modeling purposes. The RDS can be requested by contacting the EHDN Scientific Bioethics Advisory Committee (SBAC) (https://www.euro-hd.net/html/projects/proposals/scipro).

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Enroll-HD Study Status

Enroll-HD Platform Team

CHDI Management, Inc.

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 to 1) expedite the conduct of clinical trials, 2) improve the understanding of HD, and 3) foster good clinical care.

As of June 1, 2024, 31,824 participants have been recruited from 189 sites (155 are active) in 23 countries, of which 21,630 are still current (i.e., no mortality/end form) and 16.593 are active (i.e., have not missed two or more visits).

Recoded data and biosamples are made available to researchers and have already underpinned significant scientific breakthroughs. 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 were added to Enroll-HD's extended assessment battery at the sites in the United States and United Kingdom. These assessments will be available to other countries in the future.

A longitudinal collection of RNA has recently been initiated. As of May 1, two sites have been activated.

An amendment to the protocol (Enroll-HD 2.0) is underway, involving a transition from a broad recruitment approach to targeted recruitment based on the Huntington's Disease Integrated Staging System, and specific assessment batteries tailored according to disease stage.

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 Unified Huntington's Disease Rating Scale® Motor Certification (all users), FuRST 2.0 (Enroll-HD users), and Enroll-HD RNA and Plasma Collection (Enroll-HD users). Training modules also support other studies hosted by the platform. The portal successfully enables faster, cost-effective standardization of training.

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Enroll-HD: Data Quality and Performance Monitoring

Jen Ware[1] and Jenny Callaghan[2], on behalf of the Enroll-HD Platform Team

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BACKGROUND: Ensuring data quality and integrity is fundamental to the Enroll-HD study. Quality control (QC) and assurance measures are implemented and monitored at a participant, site, and study level, alongside a suite of other key performance indicators (KPIs).
AIMS: QC measures are designed to maximize data consistency, completeness, accuracy, and timeliness; KPI monitoring (including data quality indicators) facilitates efficient site management and study oversight.
METHODS/TECHNIQUES: Data quality and performance monitoring measures are centrally defined and implemented. Systems and procedures utilized include: 1) electronic data capture system; 2) remote centralized statistical monitoring (CSM) of participant data (cross-sectional and longitudinal) ; 3) remote CSM of site data, comprising KPI outlier analyses; 4) review of study level data, including tracking of recruitment, dropout, data quality, and completeness; 5) onsite monitoring to ensure compliance with protocol and applicable regulations; 6) site management underpinned by data quality measurement tools e.g., site metrics cards; 7) training, SOPs, and manuals to support data collection and monitoring.
RESULTS/OUTCOME: Data quality processes allow us to achieve and maintain a high standard of data quality, while KPI monitoring allows study staff to support sites, providing tailored support and feedback where appropriate.
CONCLUSION: Data quality and performance monitoring are critical operational processes in ensuring high quality data releases, supporting study sites, and ultimately facilitating high quality clinical research. We are currently working to unify all remote data QC procedures into a singular framework, and developing a web-based application enabling real-time centralized KPI tracking.

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Development of Assessments for Later Stage Huntington's Disease: HD-Structured Interview of Function and HD Clinical Status Questionnaire - The "Later Stage HD Assessments" Study (LSA)

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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 (by phone), 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 companions 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 HD-SIF and the HDCSQ, a questionnaire designed to capture information on disease milestones that occur during the later stages of HD.

CURRENT STATUS AND OUTLOOK: Four US sites have recruited 20 dyads in Part 1 and this part is now complete. Preliminary results from Part 1 will be available at the end of 2024. Two US sites and one UK site have recruited 17 dyads in Part 2. Part 2 began in June 2022 with preliminary results expected at the end of 2025. These assessments will be incorporated in the upcoming Enroll-HD 2.0 protocol and may be used in the future for planning studies or for other observational and interventional studies of HD.

11

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 and 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 International Parkinson and Movement Disorder 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.

EHDN is financially supported by the CHDI Foundation.

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Seed Funding by the European Huntington's Disease Network: Pump-Priming Cutting-Edge Huntington's Research

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The European Huntington's Disease Network (EHDN) is an independent non-profit organization dedicated to advancing research, conducting clinical trials, and improving care for people affected by Huntington's disease (HD). To advance research, EHDN has developed several strategies, including the implementation of the Lesley Jones Seed Fund Program, which was established in 2008. This program was designed to help support and fast-track pilot studies in Huntington's disease (HD) research required for larger funding applications at other organisations. A key aspect of Seed Funding is that the project must explore novel and original ideas that have the potential to move HD research in new directions. Funds up to €50,000 may be requested, with a broad range of activities supported from fundamental pre-clinical studies to clinical work including biomarker identification and pilot clinical trials. To date, 476 applications have been submitted, with

94 Seed Funds awarded for a total of >€3M in research funding provided. 13 countries across Europe have been supported by Seed Funds, with funded projects fostering novel collaborations across Europe and beyond. Notably, Seed Funds have supported HD researchers across all career stages. The early work supported by the Seed Funds has led to several larger studies being funded and has contributed many publications. In our presentation we will provide a detailed analysis of the Seed Fund Program to date, which will help identify the most successful aspects of the program, as well as areas that could be further refined and enhanced to better support the HD community.

KEYWORDS: EHDN, Seed Funds, Huntington's disease, research funding

13

Levocarnitine Improves Heat Stress Survival in Caenorhabditis Elegans Model of Polyglutamine Disorders

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BACKGROUND: Carnitine is a crucial fatty acid transporter and modulator of mitochondrial function. In our previous studies we identified a high prevalence (25%) of carnitine deficiency in Huntington's disease (HD) patients. However, the specific role of carnitine in HD remains unclear.

OBJECTIVE: This study aimed to evaluate the effects of levocarnitine on heat stress survival in a Caenorhabditis elegans (C. elegans) model of polyglutamine disorders.

METHODS: We utilized C. elegans strains N2, AM101, and WLZ3, representing wild type, polyglutamine disorders model (40 CAG repeats), and Parkinson's disease (PD) model, respectively. Worms were incubated at 20°C in nematode growth medium agar, with L-carnitine solutions of 200 µM and 20 mM added to the food source, while control groups received no L-carnitine. Each strain and concentration group consisted of 30-40 age-synchronized worms. The worms were exposed daily to 35°C for 3 hours and scored for survival until all had perished.

RESULTS: Survival under repetitive heat stress was significantly shorter in the polyglutamine strain compared to the wild type and PD model controls. The addition of 200 µM and 20 mM levocarnitine significantly improved survival in the polyglutamine strain ($p = 0.0092$ and 0.0011, Cohen's d effect size = 0.58 and 0.80, respectively). No significant survival benefit was observed for levocarnitine in the wild type and PD model strains.

CONCLUSIONS: Levocarnitine significantly enhances heat stress tolerance in C. elegans model of polyglutamine disorders, indicating potential beneficial utility for Huntington's disease. Further research is needed to elucidate the underlying mechanisms of this phenomenon.

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Clinical Trials Career Ladders: Growing the Future of Clinical Trials Leadership

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BACKGROUND: An ongoing issue that research centers face is managing coordinator turnover without disrupting ongoing clinical trials. Coordinator turnover happens for a variety of reasons, including opportunities for growth at research centers.

OBJECTIVE: At Georgetown University's Huntington's Disease Center for Care, Education, and Research, Center leadership noticed this issue and created and implemented a career ladder program in the summer of 2023.

METHODS: Center leadership identified three target areas of improvement that increased the overall Center work load. These target areas were: Regulatory and Data Management, Trials Budget Management, and FDA Audit Readiness. We then created two new research positions, allowing for promotional potential for staff as well as creating an educational path for coordinators and encouraging career research staff.

RESULTS: As a result of this initiative, the Center now has four research staff positions, addressing the concern of lack of growth potential for researchers as well as creating the necessary positions to manage the increased work associated with the three target areas. The Center has been able to implement a biannual internal review process for FDA Audit Readiness, as well as complete an internal review and

renegotiation of four clinical trials budgets, and implement a process management review in order to streamline research activities, thereby increasing site efficiency for patient visits and reducing the potential for protocol deviations and other regulatory issues.
CONCLUSIONS: This process could help other research sites struggling with similar work load issues, aid in trials recruitment and retention by maintaining staff consistency, and promote career options for research coordinators.
KEYWORDS: Career Ladder, Career Coordinator, Career Growth, Education, Staff Turnover

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Cognitive Impairment in Huntington's Disease: An Incomplete Picture in Medical Records

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Funding: This study was funded by Sage Therapeutics, Inc. (Cambridge, MA, USA). Medical writing and logistical support were provided by Boston Strategic Partners, Inc. (funded by Sage Therapeutics, Inc.).
BACKGROUND: Cognitive burden among patients with Huntington's Disease (HD) may not be fully represented in medical records, as HD has been traditionally defined as a movement disorder.
OBJECTIVE: This analysis from the observational RISE-HD (Real-world Integrated Evidence Study in HD) study compared cognition-related data in patients' medical records versus prospectively collected patient-reported outcomes [PROs] data.
METHODS: Retrospective review of medical records and prospective collection of PRO data were conducted (06/2022-04/2024, using PicnicHealth Pulse) among individuals diagnosed with HD or with mutant huntingtin expansion gene. Clinical history was reviewed for reporting of cognitive symptoms, assessments, and treatments; PRO data (Huntington's Disease Everyday Functioning scale [Hi-DEF]) were collected, measuring impacts of cognitive impairment on functioning.
RESULTS: Overall, 386 participants were included (mean [± SD] age at enrollment 46 [±13] years, 89% White, 66% female). Under 40% of participants had records of any cognitive assessments, most commonly Mini-Mental State Examination or Montreal Cognitive Assessment; accordingly, over the period of 3-5 years post-diagnosis, cognitive symptoms were reported among only 26%-32% of participants. Conversely, prospective data demonstrated ≥25% of participants with self-reported Total Functioning Capacity (TFC-SR) 11-13 (N=90) and ≥70% with TFC-SR 7-10 (N=79) reported difficulties on individual items of the Hi-DEF, indicating deficits in functioning due to cognitive impairment.
CONCLUSIONS: Medical records generally underrepresented cognitive burden associated with HD, which may reflect gaps in assessment (e.g., due to difficult-to-administer tools with limited sensitivity) and documentation of cognitive impairment in clinical practice. Supplementation with PRO data may help capture holistic experiences of patients with HD.

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Saccadic Adaptation Performance as a Biomarker in Pre- and Early Symptomatic Huntington's Disease

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BACKGROUND: Huntington's disease (HD) is an inherited neurodegenerative disorder associated with cognitive, psychiatric, and motor dysfunction. It has been reported that learning tasks involving reaching movements in both pre- and early symptomatic HD gene carriers are impaired, even years

before clinical disease onset.[1] Experimental tasks involving motor learning may provide an assay of disease onset and progression in HD.

OBJECTIVE: We assessed motor learning using saccadic adaptation paradigms in HD and control participants. Oculomotor learning dynamics in psychophysical paradigms such as the saccadic adaptation task are easily accessible and non-invasive, and learning dynamics may serve as a performance-based biomarker to detect early pathological changes in HD patients.

METHODS: Ten early symptomatic HD patients (Total Functional Capacity Score ≥ 10/13) and sex/age-matched controls were tested on a standard saccadic adaptation task. Eye movements were measured using infrared oculography. Learning dynamics of how quickly the participants adapted their saccade metrics were analysed using a two-state state-space modeling approach.[2, 3]

RESULTS: Initial findings demonstrate that oculomotor learning in HD patients is qualitatively slower and more variable in pre- and early-symptomatic HD gene carriers compared to controls. There were also significant differences in learning rate and retention over separate trial blocks.

CONCLUSIONS: These results demonstrate that motor learning dynamics can be captured by a saccadic adaptation task and may indicate early motor dysfunction in HD. Using state-modeling techniques, we were able to differentiate pre- and early-symptomatic HD gene carriers from controls, thus providing a dynamic and sensitive biomarker to monitor disease onset and progression.

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Emotional Reactions to Genotype Negative Results for Huntington's Disease: A Scoping Review of Qualitative Findings

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BACKGROUND: While much attention has been given to understanding the emotional responses of individuals whose genetic test is positive for Huntington's disease (HD), less is known about the experiences of those who test negative.

OBJECTIVE: This scoping review aims to address this gap by synthesizing qualitative findings on the emotional reactions to genetic testing for non-carriers of HD.

METHODS: A search of CINAHL, Scopus, OVID MEDLINE and PsycInfo databases was conducted from inception to March 15th 2024, to identify qualitative findings from mixed methods research, qualitative research and narrative literature on emotional reactions to a negative genetic test for HD. Utilizing review management software Rayyan and the PRISMA-ScR scoping review guidelines, article inclusion and themes were identified by multiple authors.

RESULTS: 26 articles were found that met our criteria. The articles were published during 1991-2021 with 12 from North America, 11 from Europe, and 3 from Australia. An overrepresentation of females was observed in the reported gender ratios. Four major themes emerged: direct emotional response (e.g. relief, shock, disbelief), readjustment of self (e.g. shifting identity, catalyst for change), impact on relationships with family and community, and the desire for more support.

CONCLUSION: Our scoping review highlights the complexity of emotional responses to a negative genetic test for HD. Findings from this review will inform healthcare providers, genetic counsellors, and researchers about the specific challenges and support needs of non-carriers for HD, facilitating more tailored person-centred care and support.

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The Frequency and Clinical Impact of Synonymous HTT Loss-of-Interruption Variants in a Diverse HD Cohort

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BACKGROUND: Synonymous variants that remove interruptions to HTT CAG and CCG repeats are known modifiers of Huntington's disease (HD) age of onset. However, the frequency and clinical impact of HTT loss-of-interruption (LOI) modifiers still need to be better defined.
OBJECTIVE: To address this, we investigated a large ancestrally diverse cohort of both reduced penetrant and fully penetrant patients.
METHODS: We screened symptomatic HD participants from the UBC HD Biobank and five research sites for sequence variants. Following variant identification, we examined the clinical impact and frequency in the reduced penetrance range.
RESULTS: Our analysis reveals that patients with CAG-CCG LOI and CCG LOI variants have a similar magnitude of earlier onset of HD by 12.5 years. Notably, these sequence variants exhibit ancestry-specific differences. Additionally, patients with the CAG-CCG LOI variant demonstrate a faster progression of Total Motor Score (TMS) by 1.9 units per year compared to canonical patients. Symptomatic patients with the CAG-CCG LOI variant show enrichment in the reduced penetrance range. Furthermore, the CAG-CCG LOI variant explains the onset of two symptomatic HD patients with diagnostic repeats below the pathogenetic range.
CONCLUSIONS: The findings have significant clinical implications for patients with the CAG-CCG LOI variant who receive inaccurate diagnoses near diagnostic cut-off ranges. Improved diagnostic testing approaches and clinical management strategies are needed for sequence variants patients. We present the largest and most diverse cohort of *HTT* CAG and CCG sequence variants and emphasize their importance in clinical presentation in HD.

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A Brain-Penetrant Small Molecule, ORI-113, Effectively Reduces Soluble Full-Length Mutant Huntingtin (mHTT), its mHTT Fragments and Insoluble mHTT Aggregates In Vivo

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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: Following a high-content, high-throughput in vitro screen, ORI-113 emerged as a promising lead that reduces mHTT protein via selective autophagy, prompting us to investigate its efficacy in vivo.

ORI-113 was well distributed in plasma, brain and muscle following systemic administration in

wild-type mice with pharmacokinetics consistent with daily dosing. YAC128 mice with a full-length mHTT transgene, exhibit observable aggregates in the brain by 12 months. Treatment of 8-week-old, pre-symptomatic YAC128 mice with ORI-113 for two weeks resulted in a significant 25% reduction of soluble full-length mHTT protein its fragments in cortex and striatum with no adverse effects observed.

R6/2 mice carrying a human mHTT exon 1 transgene rapidly develop mHTT aggregates within 2 weeks of age, exhibiting prominent HD-like symptoms at 8-10 weeks of age. Treatment of 8-week-old R6/2 mice with ORI-113 for 2 weeks resulted in a significant 27% reduction of soluble mHTT exon 1 in cortex and striatum, comparable to results in YAC128 mice. Interestingly, ORI-113 reduced insoluble mHTT exon 1 by 41% in cortex and by 42% in striatum. These data are consistent with ORI-113 preventing or reducing mHTT aggregates and suggest that reducing soluble mHTT by ~25% may be sufficient to prevent accumulation of mHTT aggregates.

CONCLUSION: In summary, ORI-113 effectively reduces mHTT protein, impedes aggregation in vivo without adverse effects, and shows promise as a brain-penetrant therapeutic for HD.

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The EHDN & MDS Huntington's Disease Fellowship Exchange Programme: Evaluation of Impact

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BACKGROUND: The clinical fellowship programme in Huntington's disease (HD) was initiated by the EHDN in 2013 and, from 2017, co-sponsored by the European section of the International Parkinson and Movement Disorder Society. The key aims of this unique programme are to (1) strengthen clinical care, (2) motivate and facilitate the training of young professionals, and (3) help establish contacts and opportunities for future collaboration.

AIMS: The Fellowship Impact Project (FIP) was developed in 2023 to evaluate the impact of the programme in meeting its objectives, identify potential gaps/issues in its provision, and make data-driven recommendations for improvement.

METHODS: Data were collected from three groups (past fellows, hosts, and the EHDN organisational support team) through surveys, one-to-one interviews, phone, email, and direct discussions. Data were analysed using descriptive statistics and qualitative analysis.

RESULTS: A large proportion of past fellows were highly satisfied with what they had learnt from the programme, the opportunities provided for collaboration, and the impact of the programme on improving their HD practice and care in their home country. Hosts appreciated the motivation and enthusiasm of fellows. The EHDN organisational support team provided new insights into the successes and challenges of programme organisation, placement of the fellows, and administration. Several recommendations were made for improvement of the programme.

CONCLUSION: The FIP confirmed the success of the fellowship programme in providing opportunities for fellows to learn about multidisciplinary HD clinics and improve their clinical knowledge and care. The recommendations received are under evaluation.

KEYWORDS: Huntington's Disease, fellowship, clinic, multidisciplinary, care

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Self-Perception of Everyday Cognition in Huntington's Disease (SPEC-HD)

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BACKGROUND: Neuropsychological batteries can comprehensively evaluate cognitive dysfunction in early Huntington's disease (HD). However, the extent to which these deficits correspond to the real-world experiences of patients and caregivers remains unclear. Thus, there is an ongoing need to develop sensitive and efficient cognitive assessments that capture the earliest self-reported cognitive symptoms that impact daily functioning in HD.

OBJECTIVE: This study aims to pilot a questionnaire designed to assess perceived cognitive difficulties in individuals with HD. This questionnaire will be iteratively refined by selecting questions that most effectively differentiate between individuals with pre-symptomatic HD (preHD) and control participants.
METHODS: Participants with known CAG repeat length and demographically-matched controls from the BIDMC HD research repository completed the initial 10-minute 44-item Likert-scale questionnaire (response range 1 (Never) to 5 (Almost Always)). Response frequency was tabulated for each question for each group. Independent samples t-tests were performed to compare group responses.
RESULTS: 16 HD and 6 control participants were included in the analysis. The highest-rated items in controls, motor-manifest HD, and preHD (Total Motor Score (TMS) ≤8) are outlined.
CONCLUSIONS: This questionnaire will undergo rigorous refinement to better understand the nuances of self-reported cognitive difficulties in early HD. Although still in the pilot phase, this tool aims to enhance the ability to reliably capture cognitive changes, contributing to meaningful endpoint monitoring and outcome assessment in clinical research focused on improving early cognitive deficits in HD.

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Prevalence of Reported Cardiac Conduction Abnormalities in Enroll-HD

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BACKGROUND: Heart disease is the second most common cause of death in patients with Huntington's Disease (HD), Stephen et al. reported that up to 43.3% of 590 early HD patients had abnormal electrocardiograms (ECGs). However, the prevalence and rate of progression of different types of cardiac arrhythmias across the entire HD spectrum remains unclear. Understanding how these problems unfold during disease progression has important clinical and research implications.
AIMS: To determine the prevalence and rate of progression of different types of cardiac conduction abnormalities across the entire HD spectrum using the largest HD observational dataset, Enroll-HD.
METHODS: Using the Enroll-HD periodic dataset (cutoff date 12-08-2020), a population of participants that reported one or more of 35 cardiac conduction abnormalities was analyzed. The prevalence was assessed across reported HD disease stages, using both CAP and TMS scores as markers of disease progression.
RESULTS: Approximately 0.40% of pre-manifest participants and 1.12% of manifest participants reported cardiac conduction abnormalities at the baseline visit. Bradycardia and cardiac arrhythmia were most common in the manifest group at approximately 1.5 and 3 times the frequency of controls, respectively.
CONCLUSION: Compared to the literature, cardiac conduction abnormalities were substantially underreported in the Enroll-HD dataset, highlighting a potential lack of awareness among patients and caregivers. Given the high prevalence and clinical risk of cardiac conduction abnormalities in this population, observational studies should make a concerted effort to better capture these important diagnoses and consider implementing routine ECGs at all visits.
KEYWORDS: Huntington's Disease, Bradycardia, Cardiac Arrhythmias

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Effectiveness and Satisfaction with Deutetrabenazine in Huntington Disease When Initiated Using a 4-Week Patient Titration Kit: Final 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 (July 2021) to assist patients in titrating to optimal deutetrabenazine dosages.

OBJECTIVE: Evaluate real-world effectiveness and patient and healthcare professional (HCP) satisfaction with deutetrabenazine, initiated using the kit.

METHODS: START was a 2-cohort (TD and HD) study evaluating real-world usage of deutetrabenazine when initiated using the kit. Final results from the HD cohort are presented.

RESULTS: 13/17 (76%) patients successfully completed the kit (completed within 5 weeks or reached optimal dose [≥24 mg/day] within 4 weeks); mean (SE) adherence rate 92% (6%). 8/16 (50%) patients achieved treatment success ("much"/"very much" improved) at Week 12 per Clinical Global Impression of Change (GIC); 10/16 (63%) per Patient GIC. Mean total maximal chorea scores decreased by 4.4 (41%) from baseline to Week 12. Among 12 (71%) patients responding to the custom patient satisfaction questionnaire at Week 8, 92% found it easy to change dosages weekly and understand when/which dosage to take, and 100% to use the kit overall. Among 7 HCPs responding to the custom HCP questionnaire, 100% found the kit helpful to ensure patient adherence to the titration schedule and 86% were satisfied with providing the kit to patients.

CONCLUSIONS: The titration kit enabled patients to titrate to optimal deutetrabenazine dosages with effectiveness similar to that of pivotal clinical trials [2, 3] and with high patient and HCP satisfaction.

ABSTRACT SUMMARY: The START study evaluated real-world usage of deutetrabenazine when initiated using a 4-week patient titration kit. As of this final analysis, 76% of patients with Huntington disease–associated chorea successfully completed the kit, with a mean adherence rate of 92%. 50% of patients achieved treatment success, and 100% of responding patients found it easy to use the kit. 100% of healthcare professionals found the kit helpful to ensure patient adherence to the titration schedule.

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PASS Pathways; and an employee and board member for the Neuroscience Education Institute.

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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 Therapeutics (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 2024, the rate of DNA donations to the UBC HD Biobank increased 20x over previous years, and tissue donations have more than doubled. We have made this integrated resource available to the HD research community with formal options for worldwide collaborative use.

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Tolerability of HTT-Lowering; Learnings from Nonhuman Primates

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BACKGROUND: Huntington's Disease (HD) is a neurodegenerative disease caused by CAG expansion in the huntingtin (HTT) gene, resulting in expression of mutant HTT protein. HTT-lowering is a potential approach for the treatment of HD actively being explored. A long-standing question is the extent to which HTT-lowering can be tolerated in adults.
OBJECTIVE: We sought to explore the tolerability of deep and sustained HTT-lowering in wild-type (wt) non-human primates (NHPs) over 6 months after single and repeated intrathecal administration of a C16-conjugated small interfering RNA (siRNA) targeting HTT.
METHODS: Tolerability of HTT-lowering was assessed in NHPs through in-life clinical observations, neurological exams, detailed histopathology assessments, and multiple CSF parameters. HTT protein levels were assessed in CNS tissues at 3- and 6-months to confirm extent of lowering.
RESULTS: Treatment of NHPs with a C16-conjugated siRNA achieved robust reduction in HTT protein expression (> 90% lowering in the cortex) and appeared to be well tolerated throughout the study period. There were no treatment-related clinical observations, abnormalities in neurological exams or histopathology assessments, and no changes in any measured CSF parameters, including NfL, total protein, and cell counts.
CONCLUSION: Our results suggest that deep, sustained lowering of HTT protein expression in the CNS of adult non-human primates by a C16-siRNA conjugate can be well tolerated for at least 6 months, supporting future clinical evaluation of C16-siRNA conjugates as a novel platform approach to HTT-lowering in the CNS.
KEYWORDS: Experimental therapeutics, HTT-lowering, siRNA

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Incorporating Social Work to Improve Clinic Attendance for Huntington's Disease Patients

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BACKGROUND: When there are high rates of non-attendance to scheduled outpatient appointments creates stress on available healthcare resources. Poor clinic attendance may be mitigated by anticipating, identifying, and removing barriers to care.
OBJECTIVES: This analysis is to determine if collaborative scheduling meetings between the clinic coordinator and social worker improve mean number of patients seen at the three MedStar/Georgetown Huntington Disease Care, Education, and Research Center clinic locations in the DC metro area. The outcome of this analysis will guide future efforts to improve clinic attendance.
METHODS: The HD-CERC Clinic Coordinator and Social Worker initiated weekly, collaborative patient scheduling meetings beginning in April 2024. Together they examined the mean number of patients scheduled for clinic visits from January 2024 – April 2024, prior to the start of joint scheduling meetings, and compared this data to the mean number of patients scheduled from May 2024 – August 2024, after joint scheduling meetings were initiated. Comparisons were not made between clinic locations due to variable clinic capacity.
RESULTS: Overall, clinic attendance increased at all three clinic locations once collaborative clinic schedule meetings were initiated. Since baseline at the start of this initiative, attendance at our two full day clinics increased by 62% and 48% respectively, while our half-day clinic increased by 5.2%.
CONCLUSION: Anticipating and resolving barriers to clinic attendance through collaborative scheduling efforts between the clinic coordinator and clinic social worker allow for the COE to meet the needs of more patients and families and improves utilization of clinic time for clinicians.

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The Centre for Neurological Rare Diseases: A New Born LIRH Foundation's Facility for People with Rare Neurological Diseases

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BACKGROUND: LIRH Foundation is a third-sector organization, founded in 2014. The three pillars of its HD focused activities are: care, research, advocacy.
AIMS: To ensure that people affected by HD have less fear of it. To provide families with proper care, to foster clinical research and stimulate participation in clinical trials, to raise awareness, to advocate for patients' needs, to contrast the mis-knowledge and the miscommunication, to turn up a light on juvenile and pediatric-onset HD, to bring younger people closer to the clinic.
METHODS: Over the last 10 years, we have been developing an 'organizational model' based on proximity to the affected families, dedicated secretariat, integrated communication, knowledge of the HD affected individuals medical and social needs, networking with other advocacy organizations, education of health care professionals.
RESULTS: Five local HD family associations became members of LIRH Foundation. HD prevalence in Italy and in the Middle East, HD disease burden for Italian families and the pediatric HD variant, were described. The number of first visits requested has been growing each year. A different narrative of HD was spread (more than 'chorea'). A specific procedure on genetic counselling was developed. A rare neurological diseases clinic was launched. The number of participants in clinical trials is doubled.
CONCLUSIONS: After 10 years of commitment, the Italian HD community is better assisted, patients are involved in clinical studies, families are more aware of the neurodegenerative impact of HD on their lives. We set the CMNR to replicate this successful model for other rare neurogenetic disorders.
KEYWORDS: Care, research, advocacy, awareness, network

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Challenging Balance and Gait Tasks May Differentiate Persons with Huntington's Disease from Non-Huntington Peers and Indicate Early Declines

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BACKGROUND: Balance is affected early in Huntington's disease (HD) and progressively worsens over time, impacting safe mobility and increasing fall risk. No outcome measure specific to balance impairments in HD exists. A better understanding of tasks that decline across HD stages may improve early detection of balance impairment and indicate treatment efficacy.
OBJECTIVE: To evaluate the known-groups validity of balance-related tasks in HD and non-HD peers.
METHODS: In a single session, we compared balance performance across non-HD peers and HD-ISS groups using ANOVA to examine tasks that differentiate between groups.
RESULTS: 36 individuals with HD (age 52.4±16.2 years; HD-ISS: stage 0-2, n=8; stage 3/mild, n=10; stage 3/moderate, n=11; stage 3/severe, n=7) and 16 non-HD peers (age 48.1±11.6) completed testing. Tasks with changed sensory input (eyes closed, foam, incline) and lateral movements differentiated non-HD peers from HD-ISS 0-3 ($p<.001$). Sequenced step-ups ($p<.035$) differentiated HD-ISS 0-2 from HD-ISS 3 while single leg standing (SLS; $p<.032$) and walking with a narrow base of support ($p<.025$) differentiated HD-ISS 0-2 and 3/mild from HD-ISS 3/moderate-severe. Walking with head turns ($p<.003$) and transitioning from forward to backward walking differentiated HD-ISS 3/severe from all other groups ($p<.044$).
CONCLUSIONS: Declines in tasks requiring sensory reweighting, lateral movements and SLS may be early indicators of balance decline that should trigger referral to physical therapy to reduce fall risk. Declines in gait may indicate further progression. This preliminary analysis lays groundwork for ongoing analyses to validate an HD-specific balance outcome measure suitable for monitoring, symptom management, and clinical trials.
KEYWORDS: Balance, postural control, gait, clinical trials

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HD Genetics: Insights from 500+ Clients of First Two Years of HD-Specific Telegenetics Service Provider

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BACKGROUND: HD Genetics has provided fully remote genetic counseling (GC) and testing options for those at-risk for Huntington's disease (HD) in the United States for two years.
OBJECTIVE: This presentation describes client insights gathered from pre-GC and post-results appointment questionnaire submissions, as well as GC records.
METHODS: HD Genetics' services begin with client submission of an online client intake questionnaire, then proceed to full GC services over a combination of phone and video appointments. Here, we provide updated frequencies of client intake questionnaire responses, appointment completion, test results, and metrics of client satisfaction from post-results appointment questionnaires.
RESULTS: As of 7/5/2024, 625 clients submitted an intake questionnaire, and 507 consented to being included in research (81%); of these, 384 (76%) completed an intake appointment, and 308 (80%) of these completed pre-test GC. Of these, 237 (77%) ordered a test kit for HD, 215 (91%) 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 beyond the initial intake appointment, and 42% tested and received their results. Of clients who have tested, 51% have tested negative, 38% positive, 6% intermediate, and 5% in the reduced penetrance range. Of clients who completed optional post-results appointment questionnaires (N=69), all reported "very likely" to recommend HD Genetics.
CONCLUSIONS: Frequencies reported here are similar to those of year one, reflecting steadiness and continued success in providing an accessible, patient-centered GC and genetic testing option for the HD community.

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Cross-Sectional Investigation of Evolving Cerebral Metabolism, Brain Volumes, and Mutant Huntingtin Aggregates in the zQ175 DN Mouse Model of Huntington's Disease

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BACKGROUND: The failure of identifying a disease modifying treatment of Huntington's disease (HD) at the manifest population may be attributed to the significant loss of 50% or more of striatal volumes observed at the onset of clinical symptoms.
OBJECTIVE: To assess the therapeutic efficacy in the absence of clinical symptoms in the zQ175 DN mice.
METHODS: To identify preclinical changes in brain metabolism and structure, the heterozygous zQ175 delta-neo (DN) mouse model at distinct ages - 3, 6, 10, and 16 months were applied. We employed T2-Relaxation-Under-Spin-Tagging (TRUST) MRI to measure cerebral metabolic rate of oxygen (CMRO2) and T2-weighted structural MRI to examine brain volumes.
RESULTS: Significant atrophy was observed in the striatum, neocortex, lateral globus pallidus, and the whole brain, in zQ175DN HD mice at 6 months of age. This brain atrophy steadily worsened with advancing age, becoming more pronounced in 10- and 16-month-old zQ175 DN mice. Additionally, we noted a declining trend in CMRO2 and oxygen extraction fraction (OEF) starting at 6 months in zQ175 DN mice comparing with age-matched controls. Substantial and progressive declines in CMRO2 and OEF were evident in the 10- and 16-month-old HD cohorts. Notably, we observed PHP1-positive mHTT aggregates by immunofluorescent staining in the striatum and cortex regions of zQ175 DN mice, with the numbers dramatically increasing with age in HD mice. Interestingly, mHTT aggregates were predominantly intranuclear before 6 months of age, while both intranuclear and neuropil mHTT aggregates were evident in the brains of 10- and 16-month-old zQ175 DN mice.
CONCLUSIONS: The location of mHTT may reflect the severity of HD pathogenesis. This study is the first to systematically characterize changes in both cerebral metabolism and brain volumes across four ages in the zQ175 DN mouse model. Our data provide crucial insights and guidance for selecting outcome measures when utilizing this HD mouse model for treatment trials.

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Antibodies from Resilient Individuals: Identifying a Potential Novel Treatment for Huntington's Disease Modification

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BACKGROUND: At Alchemab, we are harnessing the power of the immune system to counter complex diseases. Using a combination of next-generation sequencing, serum proteomics, and computational discovery, we pinpoint antibodies associated with improved outcomes. Using this approach, we discover antibodies uniquely present in individuals showing resilience to defined diseases, binding novel epitopes which may not be easily discovered using more traditional antibody discovery routes.
OBJECTIVE: To develop therapeutic antibodies for Huntington's Disease.
METHODS: The B cell repertoire of Huntington's Disease individuals was mined, and antibodies

uniquely present in individuals with extraordinarily slow disease progression identified. These antibodies were not present in individuals with standard disease progression, and were profiled in various in vitro and in vivo studies.
RESULTS: ATLX-1095 was identified as a HTT binding antibody, uniquely present in individuals with slow disease progression. It binds all tested forms of mutHTT, including aggregates, increases the phagocytosis of HTT by iPSC derived microglia and decreases aggregates without affecting endogenous HTT in the R6/1 mouse model. It has a favourable development profile, no off targets, and is in pre-clinical development. Target engagement assays developed at protein binding level (free HTT), efficacy readouts (HTT aggregates via PET ligand; NEFL), and exploratory biomarker discovery using mass spectrometry imaging, unbiased mass spectrometry and spatial transcriptomics are being utilised in translational studies to support clinical study design.
CONCLUSION: ATLX-1095 identified as novel therapeutic for Huntington's Disease. Currently in development for clinical study starting in late 2025.

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Benefits of Project Management at Study Site Level: Exploring Implications on Clinical Trial Implementation Efficiency at Georgetown University

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BACKGROUND: Clinical trials for Huntington's Disease (HD) have become increasingly complex, resulting in the need for new methods for managing trials from start up to study end. At the MedStar/Georgetown Huntington's Disease Care, Education, and Research Center (HD-CERC), we utilized project management tools to visualize all the moving pieces of clinical trials and identify challenges of running simultaneous HD studies.
OBJECTIVE: This project aimed to identify areas of improvement to help the research staff manage complex study protocols. We explored the benefit of utilizing visual tools such as process flowcharts for conducting a clinical research study. The flowchart aids in breaking down complex tasks and illustrates the steps and decisions needed to complete the task.
METHODS: The process flowchart was created using Lucidchart software. We combined institutional standard operating procedures, study-specific checklists, and vendor manuals to create one all-encompassing process flowchart for all Center research visits.
RESULTS: The study visit flowchart has proved as a beneficial tool for onboarding, training, process improvement, and planning. The tool also aids in identifying areas for growth and educational opportunities for staff. The flowchart shows how study visits are a small portion of the work load of trial implementation at a site level.
CONCLUSIONS: By creating and following the process flowchart, we are able to predict the total scope of work and ensure the study visits are completed using a standardized process, bolstering the overall efficiency and team alignment. We anticipate that, by better understanding our workflow, we will also increase our audit preparedness.

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MedStar/Georgetown Huntington Disease Care, Education, and Research Center Uber Health Transportation Program

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BACKGROUND: The MedStar/Georgetown Huntington's Disease Care, Education, and Research Center (HD-CERC) currently serves 250 Huntington's Disease (HD) patients and their families throughout Washington, DC, Maryland, and Virginia. One of the main reasons cited by patients and caregivers as to why people with HD do not receive specialty care is a lack of affordable transportation options. We estimate that there are 1,400 people in our region who have HD at this time. Based on these conservative numbers, there are 400 people at-risk in the D.C. area, 3,800 in Maryland, and over 5,000 in Virginia.
OBJECTIVE: The HD-CERC developed the Uber Health Transportation Program to better serve HD patients and families by reducing socioeconomic

burden and improving access to care. This poster will describe how we created the Program and analyze the first six months of implementation.
METHODS: Program participation begins with concerns by the Center staff of a patient's inability to access appropriate or reliable transportation for an upcoming medical appointment. We developed the Eligibility Checklist and the Evaluation of Financial Need Questionnaire to assess eligibility for program participation. The HD-CERC clinic coordinator schedules ride to/from patients next medical appointment.
RESULTS: We estimate that one quarter of our patients would utilize this service once a year for an average round trip cost of $75, with a total program cost of approximately $4700.
CONCLUSIONS: This initiative may increase the number of patients or encourage patients to return for follow up appointments with our multidisciplinary team by reducing socioeconomic burdens to obtaining care.

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Physical Therapy Neurologic Fellowships: Development and Delivery of a Movement Disorders Curriculum Across Two Sites

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BACKGROUND: There exists a paucity of physical therapists (PTs) with specialized training to manage the rapidly growing numbers of individuals with movement disorders. To address this need, an American Board of Physical Therapy Residency and Fellowship Education (ABPTRFE)-approved multi-site and multi-state Neurologic Movement Disorders PT Fellowship Program was created.
OBJECTIVE: This report outlines the development of the fellowship didactic curriculum including its key components, the collaboration between contributors, and its potential impact on the physical therapy profession.
METHODS: Curriculum development involved numerous collaborative meetings between the two fellowship directors and faculty to discuss objectives, content, delivery and evaluation. Curriculum content was primarily based off the ABPTRFE Neurologic Movement Disorders Description of Fellowship Practice and encompassed a range of neurological conditions including but not limited to chorea and Huntington's disease, Parkinson disease, dystonia, tremor disorders, and ataxia. Key resources were identified via literature reviews, the APTA, other movement disorders societies and organizations, and through experts. delivered via online didactic learning modules and two weekend in-person skill-based sessions.
RESULTS: The curriculum design leverages the subspecialist care by PTs with neurologist movement disorders specialists to elevate the comprehensive care of patients with movement disorders.
CONCLUSION: Initiation of the Neurologic Movement Disorders PT Fellowship program using a unique collaborative approach represents a significant milestone in development of multi-site postgraduate curricula and in advancing specialized care for individuals with movement disorders. By equipping PTs with this expertise, this program potentially will elevate the field and ultimately may improve the lives of individuals with movement disorders.

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Benefit of Professional Development for Clinical Trials Coordinators: A Personal Narrative

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BACKGROUND: Professional development opportunities provide clinical trials coordinators with skills to advance their careers and benefit their institutions. Georgetown University encourages professional development and higher education by providing education tuition benefits. This primary author is enrolled as a part-time student in the Clinical and Translational Research Master's program, with courses including Aspects of Drug Development, Research Ethics, and Clinical Research Administration.
OBJECTIVES: This narrative explores the primary author's personal experience seeking professional development opportunities and outlines the benefits of continued education as a clinical trials coordinator.

METHODS: This project examines the relationship between this author's daily responsibilities as a clinical trials coordinator across multiple HD studies and the coursework within her Master's program. We assess how everyday situations during participant visits match with theoretical skills learned in coursework, and how this fosters growth and the ability to take on more independent research responsibilities.
RESULTS: Since enrolling in the Master's program, this author has assumed higher level responsibilities as a clinical trial coordinator, served as primary author for multiple professional posters, and presented at investigator meetings and conferences. The applicable skills acquired from the Master's program include understanding protocol design, ethical issues in participation payment, and statistical analyses of clinical data.
CONCLUSION: Professional development is beneficial to career research staff and should be encouraged wherever possible. The benefits of coordinators combining practical experience with theoretical knowledge may also extend to patients through becoming more effective in addressing questions or concerns from potential participants as well as walking active participants through each step in their study visits.

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ALN-HTT02, a novel C16-siRNA conjugate for HTT-lowering in the CNS

Kevin Sloan, on behalf of the ALN-HTT02 program team

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Huntington's disease (HD) is characterized by a progressive decline in behavioral, cognitive, and functional abilities, for which there are no available disease-modifying treatments. ALN-HTT02 is an investigational, intrathecally-administered, small interfering RNA (siRNA) that leverages recent advances in siRNA delivery to target both wild-type and all HD-associated isoforms of the HTT messenger RNA. Utilizing our C16-siRNA delivery platform, ALN-HTT02 is designed to potently and durably reduce HTT protein expression in neurons, and thereby has the potential to alter the course of HD progression. Here, we highlight the unique properties of the platform, share learnings regarding the tolerability of HTT-lowering in non-human primates, and outline an upcoming first-in-human Phase 1b study that will aim to characterize safety and tolerability of ALN-HTT02 in patients with HD.

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Audio Analysis of Acoustic and Linguistic Features in Huntington's disease and Parkinson's disease (Audio-ND)

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BACKGROUND: Dysarthria, characterized by unclear speech articulation, is a prevalent symptom in approximately 93% of Huntington's disease (HD) patients and 90% of Parkinson's disease (PD) patients. Although the Unified Huntington's Disease Rating Scale (UHDRS®) and Unified Parkinson's Disease Rating Scale (UPDRS) record broad clinical speech changes, the automated detection of subtle speech feature variations holds promise for generating sensitive biomarkers indicative of disease onset and progression.
OBJECTIVES: This study aimed to identify and contrast speech features that differentiate HD and PD patients from healthy controls through a data-driven exploratory analysis utilizing the Canary Speech app.
METHODS: The study included 54 HD participants (prodromal, manifest) and 20 PD participants, matched with 31 healthy controls (HC) based on sex, age, and education. Participants completed an 8-minute tablet-based protocol (Audio-ND) encompassing open-ended questions, passage reading, narrative prompts, picture descriptions, and Stroop Color and Word Test (SCWT) audio recording. Various model architectures were employed alongside pre-existing feature sets to evaluate classifier accuracy.
RESULTS: Random Forest models, paired with the Trillson feature set on open-ended questions, demonstrated the highest accuracy (90%) in distinguishing PD patients from controls. Conversely, Random Forest models utilizing prosodic and linguistic features on SCWT and passage reading tasks were most

effective in differentiating HD patients from controls (84%).
CONCLUSION: The findings suggest that specific speech features captured through automated analysis can effectively distinguish between HD and PD patients and HCs. This highlights the potential of speech analysis as a non-invasive and sensitive biomarker for early diagnosis and monitoring of disease progression in neurodegenerative disorders.

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An Early Look at the Psychometric Properties of Functional Rating Scale 2.0 (FuRST 2.0)

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BACKGROUND: The FuRST 2.0 is a 24-item patient reported outcome (PRO) measure designed to detect early functional changes in Huntington's disease (HD), as current functional assessments are insufficient[1]. Its development involved focus groups, Delphi panels, cognitive pretesting, and informal regulatory advice. To obtain preliminary psychometric properties of the FuRST 2.0 we conducted FOCUS Online, a web-based study collecting the FuRST 2.0, demographic data, and a PRO version of the UHDRS® '99's Total Functional Capacity scales (TFC).
OBJECTIVE: To assess the psychometric properties of FuRST 2.0.
METHODS: FOCUS Online involves a single assessment session. People who self-identify as having HD were invited to participate online, indicating their diagnostic status, responding to questions to determine disease progression, and completing the FuRST 2.0. The study is ongoing, and the results presented here are based on an interim analysis.
RESULTS: 169 people with HD completed the FuRST 2.0 (Age [M(SD)]=49.4 (14.2) years; 56.2% female; 91% White). Item-level utility was acceptable (skewness ≤ ±1.53; no floor/ceiling effects; total-score range 0-68). Reliability indicators were adequate (Cronbach's alpha=0.96; minimum corrected Item-to-Total 0.47). IRT-based analyses demonstrated acceptable sensitivity to the underlying trait (discrimination values 1.2 - 4.1). FuRST 2.0 total score was highly correlated with the total score from a PRO version of the TFC (rho=-0.80, p<0.0005).
CONCLUSION: FOCUS Online is designed to facilitate large-scale data collection and expedite the evaluation of the FuRST 2.0. The interim analysis suggests that online data collection is feasible and the FuRST 2.0 shows acceptable utility, reliability, and sensitivity in detecting functional changes in HD.

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Web-Based Caregiver-Reported Survey of Seizures in Juvenile-Onset Huntington's Disease

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BACKGROUND: Juvenile-onset Huntington's disease (JoHD), defined as symptoms beginning before 20 years of age, often looks much different than adult-onset HD, with decreasing school performance, attention difficulties, oral motor dysfunction, gait instability, and parkinsonism. Patients with JoHD are uniquely affected by seizures. Approximately 15% have seizures as a presenting symptom, and up to 50% of JoHD patients are eventually affected by epilepsy.
OBJECTIVE: Over the last 10 years, new anti-seizure medications have been introduced and improvements made in electroencephalography (EEG), with an increased use of continuous video EEG monitoring. However, to-date, there is a paucity of understanding of the current provider practices for treating epilepsy in JoHD.
METHODS: We undertook an anonymous, web-based caregiver-reported survey distributed through

social media, email, and flyers to better understand current medication and EEG utilization and which medical providers are managing epilepsy in JoHD.
RESULTS: Preliminary results are presented. All types of seizures were reported, but absence (staring) was the most common. Valproate was the most used medication. Newer forms of home seizure rescue benzodiazepines are being prescribed, including the intranasal formulation. Most patients are being treated for epilepsy by a general pediatric neurologist. Most patients had a history of some form of long-term video EEG monitoring.
CONCLUSIONS: Limitations of the study include a low responder rate, and recruitment is ongoing. Surprisingly, no patient's seizures were being primarily managed by an epileptologist. Despite this, preliminary results demonstrate an encouraging use of newer medication formulations and utilization of long-term video EEG modalities.

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Time-Restricted Eating in Huntington's Disease: Review of the Literature and a Proposed Clinical Trial

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BACKGROUND: Recent studies suggest that time-restricted eating (TRE), a form of intermittent fasting involving daily caloric intake within a limited time window, may hold promise in the treatment of neurodegenerative diseases, including Huntington's disease (HD) [1-5]. Although TRE has shown potential, it has yet to be analyzed in persons with HD.
OBJECTIVE: Review recent literature on TRE in HD and outline our protocol for an upcoming clinical trial designed to assess the safety, feasibility, and biomarker effects of TRE in HD.
METHODS: The literature search included articles that examined the effects of any form of dietary fasting in the context of HD (animal or human). Considering the existing evidence, we propose an interventional, single-arm trial where 25 participants with early-stage HD will be asked to engage in a TRE diet for 12 weeks. We will measure adherence, body composition, biomarkers, and clinical effects.
RESULTS: Five studies of TRE in HD were identified in the literature, and the underlying physiologic mechanisms were summarized. For the proposed trial, we predict at least 20 participants will successfully implement and adhere to the diet, fat-free mass will be maintained, and plasma markers of neurodegeneration will be improved.
CONCLUSION: Using what is known of the TRE mechanism of action and current data, we expect that the diet will be safe, feasible, and may also improve biomarkers of disease progression in persons with HD. We expect this study will lay the foundation for future large-scale clinical trials to evaluate the clinical efficacy of TRE in HD.

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Cytokine levels as predictors of HD-associated neuropsychiatric symptoms

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BACKGROUND: Huntington's Disease (HD) is an inherited neurodegenerative disorder in which inflammation is believed to play a critical role. Individuals with HD often experience neuropsychiatric symptoms (NPS) such as apathy, anxiety, irritability, depression, and obsessive-compulsive behaviors (OCBs), which can appear years before the motor symptoms.
OBJECTIVE: To determine whether peripheral inflammation can significantly predict HD-related NPS.
METHODS: 55 individuals [16 controls/39 HD gene expansion carriers (HDGECs), 36 females, age=47.5±11.8 years] underwent the Problem Behaviors Assessment-Short Version (PBA-s) and peripheral blood draw. Plasma levels of inflammatory cytokines [interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p70, IL-13, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α were simultaneously assessed using bead-based immunoassay]. Logistic regression models were used to determine the effects of age, sex, HD genetic status, and inflammatory cytokine levels on the PBA-s symptom domains (affect, irritability/aggression, perseveration/OCBs, and apathy).
RESULTS: Female sex, HDGEC, higher levels of IFN-γ, and lower levels of IL-4 were found to be significantly associated with worse affect symptoms. Female sex, HDGEC, and higher levels of IL-1β were significantly associated with irritability/aggression. Female sex was also significantly associated with apathy. Age and HDGEC were significantly associated with worse perseveration/OCBs. The models were significant, with areas under the curve varying 0.822–0.891 in the ROC analyses.
CONCLUSIONS: Female sex and HD genetic status are the most important predictors of NPS. Increased levels of proinflammatory (IFN-γ and IL-1β) and decreased levels of anti-inflammatory (IL-4) cytokines are also significant predictors of HD-related NPS.

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Validation of Remote Collection and Quantification of Blood Neurofilament Light in Neurological Diseases

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BACKGROUND: Promising blood-based biomarkers of neuropathology have emerged with the potential for therapeutic development and disease monitoring. Remote sampling for biomarker assessment could ease the burden of in-person clinical visits and allow for frequent sampling.
OBJECTIVE: We evaluated a capillary finger-prick collection method for remote quantification of blood neurofilament light (NfL), a blood-based biomarker evident in various neurological disorders, and other exploratory markers of neuronal injury and neuroinflammation (GFAP, tau).
METHODS: Matched samples from venepuncture and finger-prick were collected and processed into plasma and/or serum to directly compare NfL levels from a primary cohort of n=113 neurological patients (n=29 premanifest Huntington's Disease (preHD), n=30 symptomatic Huntington's Disease (HD), n=34 Multiple Sclerosis (MS), n=7 Amyotrophic Lateral Sclerosis (ALS), n=13 Parkinson's Disease (PD)) and n=40 healthy controls. In the discovery cohort, two delayed processing conditions were compared, three- and seven-day delay, simulating ambient shipment. We recruited a confirmatory cohort of n=121 participants (n=64 preHD and n=57 healthy controls from the HD Young Adult Study) to validate the method.
RESULTS: Capillary NfL and GFAP concentrations were equivalent to those in venous blood serum and plasma. Only NfL remained stable after seven-day processing delay. Capillary NfL replicated disease group differences displayed in venous blood. Findings were replicated in the confirmatory cohort.
CONCLUSIONS: This data supports our finger-prick method for remote collection and quantification of NfL. With the widespread applications for NfL across the spectrum of neurological disorders, this has the potential to transform disease monitoring, prognosis, and therapeutic development within clinical practice and research.
KEYWORDS: Neurodegenerative diseases, Biomarker, NfL, GFAP, Remote sampling, Finger-prick

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A Preliminary Exploration of the Social Determinants of Health Impacting Aboriginal Australians Living with Huntington's Disease in Far North Western Australia

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BACKGROUND: Aboriginal Australians face disparity in healthcare access due largely to the ongoing impacts of colonisation. Social determinants of health (SDH) reflect how significant public health concerns must be considered within a context beyond the individual. A large Aboriginal kinship living in remote far north Western Australia are affected by Huntington's disease (HD) but lack accessible specialist services.
OBJECTIVE: This study aimed to use a systems thinking approach to explore the SDH impacting the capacity of an Aboriginal Australian community to engage with the Far North Huntington's Mobile Clinic (FNHMC).
METHODS: Ethnographic exploration of the SDH impacting the affected community was conducted through observation, and yarning with clients, health service providers, and locals. Reflexive thematic analysis was employed to review field notes.
RESULTS: Preliminary analysis identified language, HD stigma, chronic disease, and health-related trauma as meso level SDH. Key micro level SDH were school truancy and low literacy, high rates of violence, and alcohol and substance abuse. Macro level SDH were cultural norms regarding wholistic views of health, relationship to country, intergenera-

tional trauma and disadvantage, and transient health staff.

CONCLUSIONS: Addressing the complex sociocultural SDH influencing the ability of Aboriginal Australians to access HD care will require consistent, community-driven, education and in-person care for decades. FNHMC staff should address HD from an holistic collective perspective, viewing healthcare decisions as both individual and community decisions. Collaborations with local service providers and community champions must be cemented to ensure broader socioeconomic factors are addressed in the development of a sustainable clinical intervention.

KEYWORDS: Aboriginal Australians; social determinants of health; public health

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Introducing the Pre-HDBOI Study: Quantifying the Clinical, Humanistic and Economic Burden of Pre-Manifest Huntington's Disease

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BACKGROUND: Pre-motor manifest Huntington's Disease (HD) is an under-researched disease area, where a multidimensional burden may already be present [1, 2].

OBJECTIVE: The objective of the Pre-HDBOI study is to explore the clinical, humanistic and economic burden in people with pre-motor manifest HD (PwPHD) in the USA and across Europe.

METHODS: The Pre-HDBOI study will be descriptive, utilising two online data collection instruments: a PwPHD Survey (PS), completed by PwPHD; and a Health Care Professional Survey (HCP-S), completed by medical specialists. The PS will collect data on the clinical profile, resource use, and impact of symptoms on the PwPHD quality of life and productivity. It will also capture early preferences of PwPHD for emerging treatments. The HCP-S is a unique survey per physician, to provide general information about the PwPHD at their practice, their clinical burden, identified unmet needs, etc.

To ensure the study design robustness, a panel of Key Opinion Leaders and representatives from Patient Advocacy Groups will provide guidance throughout.

RESULTS: First expert meeting took place in Q1 2024, with questionnaires underway. Fieldwork will start in Q3 2024 and the target sample size is 180 PwPHD and 30 HCP. Study report to be completed by Q1 2025.

CONCLUSION: This study aims to examine the burden in PwPHD, building upon insights from the Huntington Disease Burden of Illness study (HD-BOI), centred on the HD motor-manifest population. The Pre-HDBOI study will further our understanding of the multi-dimensional burden experienced by people with HD, as they move through the different disease stages.

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HD Genetics & CenExcel RMCR: Results of Partnership for Clinical Study Recruitment of 80 Individuals

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BACKGROUND: On 8/5/2022, HD Genetics began offering a fully remote genetic testing and counseling option for those at-risk for Huntington's disease (HD) in the USA. In December 2023, HD Genetics partnered with CenExcel RMCR to connect clients with a clinical trial coordinator (Liza Heap, CRC) for education about clinical studies.

OBJECTIVE: This presentation demonstrates how the HD Genetics platform can be used to recruit for clinical studies.

METHODS: HD Genetics contacted tested clients to gauge interest in HD clinical studies. Starting in January 2024, HD Genetics began asking clients in post-results follow-up calls if they'd like to learn more about HD clinical studies. Those interested were sent an email connecting them with CRC to allow them to schedule a phone conversation.
RESULTS: As of 7/10/2024, 80 individuals were referred to CRC. Of these, 44 (55%) had tested HD positive with CAG > 40, 29 (36%) tested HD negative with CAG < 27, 5 (6%) had tested with an intermediate or reduced penetrance allele at 27-39 CAG, and 2 (2%) were untested. Of those referred, 60 (80%) connected with CRC; 49 did not currently qualify for a study but were referred to participate in Enroll-HD, and 2 were randomized and enrolled into Sage's DIMENSION study.
CONCLUSIONS: As new clinical studies seek presymptomatic participants and those with earlier disease onset, new ways to recruit will be needed. This pilot partnership shows that HD Genetics can locate and connect potential participants through partnerships with HSG® clinics, CROs, and pharmaceutical sponsors.

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Contributions of Chorea to Changes in Mobility and Motor Function

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BACKGROUND: Huntington's disease (HD) causes involuntary (i.e., chorea) and voluntary motor impairments resulting in balance and mobility problems contributing to falls.
OBJECTIVE: We explored the contributions of the TMS chorea and mobility subscale scores to changes in mobility and relationships of clinical balance and mobility measures to fall risk.
METHODS: 77 individuals (18-90 years old) diagnosed with HD who were assessed by a neurologist and a physical therapist between 1/1/2015 to 6/31/2022.
A retrospective chart review extracted measures of disease progression (i.e., UHDRS®- TMS, TMS chorea and TMS mobility subscale scores, Total Functional Capacity); mobility and balance (i.e., gait speed, Tinetti Mobility Test (TMT), Functional Gait Assessment (FGA), Single Limb Stance Time (SLST)), and number of self-reported falls in the last 6 months. Repeated Measures, mixed-effects regression models controlling for age, sex, and years from onset and Spearman rank correlation coefficients were used.
RESULTS: There was no association between TMS chorea or mobility subscale scores and other formal measures of mobility and balance. However, the correlation between chorea scores and SLST approached significance (beta (SE)=0.14 (0.08), p=.077). SLST, TMT and FGA were all related to fall risk, with a 3 second decrease in SLST associated with 14% increased odds of a fall.
CONCLUSIONS: Chorea does not appear to be a primary contributor to changes in mobility and safety in individuals with HD. The TMS mobility subscale items measure a limited aspect of mobility function and further measures such as SLST may be warranted to better guide therapy interventions.

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Effects of Valbenazine on Emotional Health and Psychiatric Stability in Adults with Huntington's Disease

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BACKGROUND: Once-daily valbenazine is approved for chorea associated with Huntington's dis-

ease (HD). Disruptive neuropsychiatric symptoms are common in HD [1].

OBJECTIVE: To evaluate emotional health and psychiatric stability in participants taking valbenazine (≤80 mg/d) or placebo in the 12-week KINECT®-HD (NCT04102579) trial [2].

METHODS: Score changes from baseline (CFB) to maintenance (average of Wk10/Wk12 scores) were analyzed post hoc for each item of the Huntington's Disease Health Index (HD-HI) Emotional Health subscale [3]. Mean CFB was analyzed in "affected" participants with baseline item scores ≥2 (affected "a little" to "severely"). Safety assessments included adverse events of special interest (AESIs), the Hospital Anxiety and Depression Scale (HADS), and the Columbia-Suicide Severity Rating Scale (C-SSRS).

RESULTS: In the full-analysis set (N=125), HD-HI Emotional Health items with the largest mean CFBs with valbenazine relative to placebo were anger (-1.6 vs. -0.2 [n=46 affected participants]), feeling of being overwhelmed (-1.8 vs. -0.5 [n=54]), crankiness (-1.3 vs. -0.5 [n=50]), reduced enjoyment with activities (-1.3 vs. -0.5 [n=58]), frustration (-1.3 vs. -0.5 [n=61]), and anxiety (-1.3 vs. -0.6 [n=62]). In the safety population (N=127), 5 participants (3 valbenazine, 2 placebo) reported AESIs related to depression or suicidal ideation. HADS CFB and C-SSRS shifts from baseline indicated no worsening in anxiety symptoms, depression symptoms, or suicidal ideation with valbenazine.

CONCLUSIONS: Some aspects of emotional health appeared to improve with valbenazine in affected participants, and psychiatric symptoms did not worsen overall. Relationships between motor and psychiatric symptoms will be further explored in the long-term extension study (KINECT-HD2: NCT04400331).

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Efficacy of Valbenazine for Chorea Associated with Huntington's Disease: Subgroup Analyses of KINECT®-HD Results

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BACKGROUND: Once-daily valbenazine is approved for chorea associated with Huntington's disease (HD).

OBJECTIVE: To assess the effects of valbenazine (≤80 mg/d) versus placebo in subgroups of participants from the phase 3 KINECT®-HD study (NCT04102579).

METHODS: Analysis for the primary endpoint was the least-squares mean (LSM) change from screening/baseline to maintenance (average of Wk10/12 assessments) in the UHDRS® Total Maximal Chorea (TMC) score, with statistical significance based on the LSM difference (LSMD) between valbenazine and placebo. TMC changes were also analyzed in subgroups, categorized by demographics and baseline assessment scores as follows: sex (male, female); age (<65y, ≥65y); body mass index (<25, 25 to <30, ≥30 kg/m^2); Clinical Global Impression of Severity (<4, ≥4 [moderate or worse]); Patient Global Impression of Severity (<3, ≥3 [moderate or worse]); Anosognosia Scale (<6 [absent], ≥6 [present]); UHDRS Total Functional Capacity (11 to 13 [early-stage], 3 to 10 [mid-to-late-stage]); UHDRS Total Motor Score (≤32, >32 [>median]); and UHDRS TMC (≤12, >12 [>median]).

RESULTS: In the full analysis set (N=125, placebo=61, valbenazine=64), LSM changes for TMC score indicated significantly greater chorea improvements for valbenazine versus placebo, with an LSMD at maintenance of -3.2 (95% CI: -4.4 to -2.0; P<0.0001). TMC changes favored valbenazine over placebo in all 19 subgroups, with LSMDs (95% CI) ranging from -4.5 (-6.6 to -2.4) to -1.6 (-4.1 to 0.8). The 95% confidence intervals for all subgroup LSMDs encompassed the primary endpoint LSMD (-3.2).

CONCLUSIONS: Valbenazine was consistently effective in reducing chorea compared to placebo, with no differential treatment effects across subgroups.

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Somnolence-Related Events Over Time with Valbenazine Treatment for Chorea Associated with Huntington's Disease

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BACKGROUND: Once-daily valbenazine is approved to treat chorea in adults with Huntington's disease. In the Phase 3, double-blind KINECT®-HD (NCT04102579) study, somnolence was the most commonly reported treatment-emergent adverse event (TEAE) with valbenazine.
OBJECTIVE: To present somnolence-related events over time from KINECT-HD and the ongoing open-label KINECT®-HD2 (NCT04400331) study.
METHODS: Participants received once-daily valbenazine (starting dose: 40mg; target maintenance dose: 80mg) for 12wks (KINECT-HD) or ≤156wks with an optional 2-year extension (KINECT-HD2). Both studies included an 8-week dose-adjustment period followed by maintenance treatment. TEAEs were monitored throughout both studies; ≤52wks of follow-up data are presented for the ongoing KINECTHD2 study. Somnolence-related TEAEs included somnolence, fatigue, hypersomnia, lethargy, and sedation; analyses were based on TEAE onset date.
RESULTS: In KINECT-HD, 20/64 (31%) participants receiving valbenazine experienced ≥1 somnolence-related event (23 total events). In KINECT-HD2, 59/125 (47%) participants receiving valbenazine experienced ≥1 somnolence-related event (78 total events). All somnolence-related events were mild (KINECT-HD: 18/23 [78%]; KINECT-HD2: 58/78 [74%]) or moderate (KINECT-HD: 5/23 [22%]; KINECT-HD2: 20/78 [26%]). Onset of somnolence-related events was mostly reported in the first 2 weeks following valbenazine initiation, with lower incidences reported during maintenance treatment. Due to somnolence-related events, some participants had valbenazine dose reductions (KINECT-HD: 7/64 [11%]; KINECT-HD2: 26/125 [21%]) or discontinued valbenazine treatment (KINECT-HD: 1/64 [2%]; KINECT-HD2: 7/125 [6%]).
CONCLUSIONS: Somnolence-related events, which were generally mild, occurred early in KINECT-HD and KINECT-HD2, following initiation of valbenazine treatment. The majority of participants experiencing somnolence continued treatment with valbenazine, some with dose reductions. More research will help elucidate characteristics of somnolence in these studies.

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Efficacy of Once-Daily Valbenazine in Adults with Chorea Associated with Huntington's Disease: Effect Size Over Time

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BACKGROUND: Once-daily valbenazine is approved for treatment of chorea in adults with Huntington's disease (HD). In the phase 3 KINECT®-HD (NCT04102579) study, valbenazine significantly improved chorea versus placebo in adults with HD, as assessed by the Unified Huntington's Disease Rating Scale (UHDRS®) Total Maximal Chorea (TMC) score.
OBJECTIVE: To assess treatment effect sizes of valbenazine for HD chorea using data from KINECT-HD.
METHODS: Participants were randomized 1:1 to once-daily valbenazine or placebo for 12 weeks. Valbenazine was initiated at 40mg, then increased to 60mg (after Wk2) and 80mg (after Wk4); partici-

pants were then maintained at their highest tolerated dose (target dose: 80mg) through the remainder of treatment. TMC scores were analyzed as mean change from screening/baseline (average of screening/baseline assessments) at all post-baseline visits (Wk2 through Wk12) and at maintenance (average of Wk10/Wk12 assessments). Statistical significance was based on the least-squares mean difference (LSMD) between valbenazine and placebo. Effect sizes (Cohen's *d*) were calculated based on mean difference between valbenazine and placebo at each post-baseline timepoint.
RESULTS: The full analysis set included 125 participants (valbenazine=64, placebo=61). Compared to placebo, valbenazine improved TMC scores as early as Wk2, at the initial 40-mg dose (LSMD=-1.3, P=0.0077; d=0.49). Effect sizes generally increased over time, with a large effect size at maintenance (primary study endpoint; LSMD=-3.2, P<0.0001; d=0.93).
CONCLUSIONS: Compared to placebo, valbenazine effectively treated HD chorea as early as Wk2 at the initial 40-mg dose. Effect sizes for valbenazine generally increased throughout the 12-week trial to a large effect size at maintenance.

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Twelve-Month 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

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BACKGROUND: Huntington's disease (HD) is caused by expansion of cytosine-adenine-guanine (CAG) trinucleotide repeats in the huntingtin (*HTT*) gene which leads to the ubiquitous expression of toxic mutant huntingtin protein (mHTT). PTC518 is a splicing modifier that promotes inclusion of a pseudoexon (psiExon) containing a premature stop codon, leading to *HTT* messenger RNA degradation and lowering HTT levels. PIVOT-HD is a global, Phase 2, randomized, placebo-controlled, multidose study to evaluate PTC518 in participants with HD (NCT05358717/2021-003852-18).
OBJECTIVES: Here we will present safety, clinical, and biomarker results from the planned interim readout of PIVOT-HD that includes 12-month data for 32 participants.
METHODS: Participants with HD were randomized to receive PTC518 5 or 10 mg or placebo once daily for 12 months at 24 centers. Primary endpoints are the safety profile and the change from baseline in blood HTT at Month 3.
RESULTS: In an interim analysis of 12-month data from 32 patients who received PTC518 or placebo, PTC518 treatment resulted in dose-dependent and durable lowering of mHTT protein in the blood and cerebrospinal fluid (CSF). In addition, favorable trends were demonstrated on several relevant HD clinical assessments including Total Motor Score (TMS), Total Function Capacity (TFC), and Composite Unified Huntington's Disease Rating Scale (cUHDRS®). Furthermore, following 12 months of treatment, PTC518 has no safety signal identified to date and no treatment-related spikes in plasma or CSF neurofilament light chain protein.
CONCLUSIONS: These interim results continue to demonstrate that PTC518 is a potential therapeutic benefit in patients with HD.

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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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BACKGROUND: Huntington's disease (HD) is caused by expansion of cytosine-adenine-guanine (CAG) trinucleotide repeats in the huntingtin (*HTT*) gene which leads to the ubiquitous expression of toxic mutant huntingtin protein (mHTT). PTC518 is a splicing modifier that promotes inclusion of a pseudoexon (psiExon) containing a premature stop codon, leading to *HTT* messenger RNA degradation and lowering HTT levels. PTC518 is being evaluated in two Phase 2 studies: the 12-month PIVOT-HD study (NCT05358717/2021-003852-18) and the

PIVOT-long-term extension (LTE) study (NCT06254482).
OBJECTIVES: PIVOT-LTE is a Phase 2, double-blind, randomized extension study to evaluate the long-term safety and efficacy of PTC518 in participants with HD.
METHODS: After completing treatment in PIVOT-HD, all participants have the option to rollover into PIVOT-LTE. The primary outcome measures of the LTE are the safety profile of PTC518 through Month 30 and the change from baseline in blood HTT over time. The effects of PTC518 on blood and cerebrospinal fluid biomarkers will also be determined. Participants will receive PTC518 in PIVOT-LTE at the same dose level they received in PIVOT-HD. Those who received placebo in PIVOT-HD will receive active treatment (PTC518) at the dose level corresponding to their randomly assigned treatment group in PIVOT-HD.
RESULTS: Here we provide an update of PTC518 development and the PIVOT-LTE study.
CONCLUSIONS: Early data from PIVOT-HD indicate PTC518 treatment saw a dose-dependent reduction of mHTT in blood and CSF and was well tolerated. Enrollment of participants for PIVOT-LTE is ongoing and data will be presented at a later timepoint.

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Exploring the Role of Peripheral Inflammation in the Pathophysiology of Behavioral Symptoms of HD

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BACKGROUND: Inflammation has long been hypothesized to contribute to Huntington's disease (HD) pathophysiology. Increased peripheral inflammation has been implicated in 'sickness behavior,' a set of adaptive behaviors in response to an infection or a traumatic lesion that results in changes in mood/motivation, appetite, and sleep. Psychiatric and/or behavioral symptoms are essential components of HD, yet their underlying mechanisms are not fully understood.
AIMS: to determine whether peripheral inflammation is associated with behavioral symptoms in HD.
METHODS: 39 HD gene expansion carriers (HDGECs, 21 manifest, and 18 premanifest) underwent clinical evaluation that included motor (UHDRS®), cognitive (SDMT), and behavioral (PBA-s) assessments. Peripheral blood was drawn, and plasma levels of the inflammatory cytokines [interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p70, IL-13, interferon (IFN)-γ and tumor necrosis factor (TNF)-α] were simultaneously assessed by bead-based immunoassay. We performed principal component analysis (PCA) and k-means clustering with a predetermined optimal number of clusters (elbow method) to identify subgroups of HDGECs based on their levels of cytokines and PBA-s scores.
RESULTS: We identified two clusters that clearly distinguished individuals based on their levels of circulating inflammatory cytokines and behavioral symptoms. These clusters did not differ regarding age, sex, CAG repeats, disease stage (premanifest vs. manifest), or clinical scores (UHDRS®, SDMT). Conversely, they did show significant differences in all PBA-s domains (depression, irritability/aggression, apathy, psychosis, and executive function).
CONCLUSIONS: Our findings indicate that peripheral inflammation is associated with behavioral symptoms in HD, akin to cytokine-induced 'sickness behavior'.

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Behavioral Characteristics of Adult versus Late-Onset Huntington's Disease

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BACKGROUND: Most Huntington's Disease (HD) patients exhibit symptoms in adulthood, commonly between 30 and 50 years old, known as Adult-Onset HD (AOHD). Late-Onset HD (LOHD) is defined as age at onset ≥60. Behavioral characteristics between AOHD and LOHD have not been well defined and could help further understanding of HD in aging individuals.
OBJECTIVE: To assess reported behavioral differences at baseline between AOHD and LOHD individuals.

METHODS: 2442 individuals aged 18-59 and 372 individuals aged ≥60 with symptomatic HD onset were examined at baseline using the ENROLL-HD dataset (Version 5, US data only). Incomplete data sets were removed. Comparisons between groups were completed using t-tests.
RESULTS: LOHD individuals had shorter CAG repeats (40.7 vs 44.4, p=0.001) and reported fewer behavioral symptoms as part of their medical history. The LOHD group reported lower rates of depression (65.97% vs 57.80%, p=0.0012), irritability (61.7% vs 52.68%, p=0.0005), disruptive behaviors (31.5% vs 18.5%, p=0.0001), apathy (52.6% vs 43.8%, p=0.0006), and perseveration (50.7% vs 40.3%, p=0.0001). There was no difference in rates of psychosis or in TFC scores. AOHD had lower agreement with family members when reporting first symptoms (25.7% vs 19.7%, p=0.0037).
CONCLUSIONS: LOHD individuals may experience fewer behavioral symptoms prior to manifestation than individuals with AOHD.

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Preliminary Results of Home-Based tDCS for Neuropsychiatric Symptoms of Huntington's Disease: an Open-Label Study

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BACKGROUND: Neuropsychiatric symptoms (NPS) are important aspects of Huntington's disease (HD) [1]. Existing treatments for HD-related NPS provide limited results [2]. Studies on transcranial direct current stimulation (tDCS) have indicated potential for improving mood symptoms in psychiatric conditions [3]. We hypothesize that home-based tDCS can help alleviate NPS in HD.
OBJECTIVE: To investigate the impact of tDCS on NPS in HD.
METHODS: Open-label trial with 5 individuals [2 females, median age = 57 years (range 24-74)]. Participants received daily 30-minute tDCS sessions for four weeks (bi-frontal, 2.0 mA current, anode on the left side). NPS were evaluated at baseline, week 4, and week 8 (i.e., four weeks after the treatment).
RESULTS: After 4 weeks of treatment, there was a decrease in the mean scores of all NPS assessments. The PHQ-9 [4] scores decreased by 35.3%, and the HADS [5] Depression and Anxiety scores decreased by 41.9% and 52.9%, respectively. The bDAS [6] score decreased by 25.4%, and the CIRQ [7] score decreased by 46.1%. The PBA-S [8] Affect, Irritability/Aggression, and Apathy scores decreased by 35.3%, 92.3%, and 63.6%, respectively. The mean bDAS score continued to decrease 4 weeks after tDCS treatment. All other NPS assessment mean scores increased after the end of treatment. However, except for HADS Anxiety and the PBA-S Affect scores, all other NPS assessments maintained lower mean scores on week 8 compared to baseline.
CONCLUSIONS: These preliminary results suggest that tDCS could be a promising approach for managing NPS in HD, particularly for depressive and anxiety symptoms.

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The Effect of Antidopaminergic Medications on Huntington Disease (HD) Function, Cognition, Motor Signs, and Progression

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BACKGROUND: Antidopaminergics (ADMs; VMAT2 inhibitors and neuroleptics [off-label), are used for the symptomatic treatment of HD and are associated with faster rates of decline. No prospective, double-blind studies have assessed the long-term effects of ADMs on HD progression.
OBJECTIVE: To assess the effect of ADMs on rates of function, cognition, motor signs, and progression in HD (TMS ≥ 20, DCL=4, TFC ≥ 7, IS ≤ 90) using the ENROLL-HD database.
METHODS: Causal analysis was performed using a new-user design to account for use history. Participants were off medication at baseline, but the exposure group (N = 380) was on ADMs for the 2-year follow-up, whereas the unexposed group (N = 792) remained off ADMs. Target maximum likelihood estimation was used to estimate the mean difference of the groups adjusting for 28 confounders. 99% CIs were used for inference.
RESULTS: Participants on ADMs had a significantly faster decline at 2 years compared to those off ADMs for TFC (Δ-0.66, 99% CI [-1.04, -0.28]), SDMT (Δ-1.99 [-2.90, -1.07]), SWR (Δ-2.92 [-4.80, -1.04]), and cUHDRS® (Δ-0.64 [-.96,-.32]). The on-ADM group had improvement in chorea but worsening on the bradykinesia scale (Δ0.87 [0.02, 1.72]), gait and balance (Δ0.24 [-0.02, 0.50]), and hand movements (Δ0.53 [-0.01, 1.07]). Similar worsening was also found for subjects on VMAT2 inhibitors or neuroleptics alone.
CONCLUSION: ADM use was associated with faster progression of functional, cognitive, cUHDRS and motor performance. These observations have important implications for the conduct and interpretation of investigational studies of disease modifying agents in HD and for medical practice.

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The Phase 3 PROOF-HD Trial Demonstrates Significant Benefits of Pridopidine on Progression, Cognition, and Motor Function in Huntington Disease (HD)

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BACKGROUND: Pridopidine is a potent sigma-1 receptor agonist in development for HD.
OBJECTIVE: Evaluate the safety and efficacy of pridopidine (45mg bid) in participants with HD (TFC≥7).
METHODS: Key endpoints were change in total functional capacity (TFC) and progression (cUHDRS®), at different timepoints. Additional endpoints included Q-Motor, cognition (SWR), and Quality-of-Life (QoL).

Prespecified subgroup analyses excluded participants on antidopaminergic medications (ADMs; VMAT2 inhibitors and neuroleptics) as they are associated with faster progression, functional and cognitive decline in HD.

RESULTS: Pridopidine was well tolerated with a safety profile comparable to placebo.

In participants off ADMs, pridopidine was superior to placebo across key measures (cUHDRS, TFC, SWR and Q-Motor) at all timepoints through 78 weeks. Pridopidine showed unprecedented significant improvements from baseline compared to placebo in cUHDRS (wk26 (Δ0.46, p=0.006), wk39 (Δ0.60, p=0.003), wk52 (Δ0.43, p=0.04)); SWR (wk26 (Δ3.32, p=0.03), wk39 (Δ4.14, p=0.02), wk52 (Δ4.22, p=0.02)) and Q-Motor finger tapping IOI (wk26 (Δ-31.96, p<0.0001), wk52 (Δ-22.84, p=0.04)), for at least 1 year. Early improvements in Q-Motor are highly predictive of later benefits in function and cUHDRS. Pridopidine preserves QoL through week 78.

Pridopidine inhibits CYP2D6 and its concomitant use with ADMs (CYP2D6 metabolized) increases exposure of ADMs. In this trial, participants on lower doses of ADMs (per regulatory labels), maintain positive benefits of pridopidine and can be used for treatment of chorea and behavioral disorders together with pridopidine.

CONCLUSIONS: Pridopidine shows consistent, sustained, and clinically meaningful benefits across multiple endpoints including function, disease progression, cognition, motor and QoL in subjects off and on low doses of ADMs.

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Pridopidine Demonstrates Consistent Improvements in Q-Motor Measures and Early Benefits in Q-Motor Predict Long-Term Changes in Function and cUHDRS® in PROOF-HD

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BACKGROUND: Q-Motor is an objective measure of motor function that is centrally read, lacks inter- and intra-rater variability, shows high reliability, and has minimal or no placebo response. Q-Motor shows consistent baseline correlations with core, independent clinical endpoints including, cUHDRS, TFC, TMS, SWR, SDMT, CAP-scores and brain-volume.

OBJECTIVE: To assess the efficacy of pridopidine in Q-Motor measures in participants from the PROOF-HD study.

METHODS: Q-Motor tests "finger tapping" (FT, digitomotography) and "pronation/supination" (PS, dysdiadochomotography) were collected and analyzed blindly and centrally.

RESULTS: In all subjects, irrespective of antidopaminergic medication (ADM [neuroleptics and VMAT2 inhibitors]) use, Q-Motor measures favored pridopidine at all timepoints through 78 weeks. In subjects off ADMs, pridopidine's benefit is greater in all Q-Motor measures assessed, including FT inter-onset interval (IOI) mean (26-weeks, p<0.0001; 52-weeks, p=0.017; 65-weeks, p=0.013; and 78-weeks, p=0.003). Similar improvements are observed in PS Inter-Tap-Interval (ITI) and IOI mean.

Early changes in Q-Motor (26 weeks) are highly predictive of long-term changes in numerous clinical measures, including TFC and cUHDRS (≥52 weeks). An incremental clinical benefit in TFC (52-weeks 0.24, p=0.004; 65-weeks 0.23, p=0.009; 78-weeks 0.35, p=0.0006) is observed per 40 msec improvement in Q-Motor FT IOI at week 26. The predictability of Q-Motor measures is irrespective of ADM use and is also seen at other levels of Q-Motor improvement.

CONCLUSIONS: Pridopidine demonstrated improvements in Q-Motor assessments at all timepoints irrespective of ADM use, with strongest and most significant effects in subjects off ADMs. Early benefits in Q-Motor were predictive of long-term benefits on key clinical outcome measures of disease progression.

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Integrated Efficacy Analysis of Four Randomized Placebo-Controlled Trials Supports Pridopidine's Treatment Benefits Across Key Clinical Measures of Huntington's Disease

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BACKGROUND: In PROOF-HD, pridopidine improved measures of HD progression (cUHDRS®), function (TFC), cognition (SWR), and motor (Q-Motor) in patients off and on low dose antidopaminergic medications (ADMs).
OBJECTIVE: Determine if an integrated analysis of four studies assessing pridopidine (45mg bid) is consistent with PROOF-HD.
METHODS: An analysis was performed on HD patients (TFC≥7) off ADMs (placebo n=227; pridopidine n=208) from four double-blind trials (HART, MermaiHD, PRIDE-HD and PROOF-HD).
RESULTS: Pridopidine shows robust improvement vs placebo in TFC through week 78, reaching significance at wk26 (Δ0.31, p=0.03), 39 (Δ0.43, p=0.01), 52 (Δ0.38, p=0.02), and 78 (Δ0.49, p=0.02). cUHDRS excluding SWR (similar in sensitivity to cUHDRS) was used as PRIDE-HD did not measure SWR. Pridopidine demonstrates meaningful benefits in cUHDRS$^{(-SWR)}$ through week 78, reaching significance at wk26 (Δ0.30, p=0.006), 39 (Δ0.45, p=0.002), and 52 (Δ0.29, p=0.04). All trials contribute positively to the observed benefits.

Pridopidine improves all measures of Q-Motor Finger Tapping (FT) and Pronation/Supination (PS). These include significant benefits in FT IOI through 78 weeks: wk12 (Δ-31.03, p=0.047), 26 (Δ-26.68, p<0.001), 52 (Δ-25.27, p=0.017), 65 (Δ-20.66, p=0.050), and 78 (Δ-25.13, p=0.022). Importantly, pridopidine shows improvements from baseline at wk12 (Δ-19.42) and wk26 (Δ-12.06). Similar benefits are seen for PS.

Pridopidine with low dose ADMs (per the regulatory labels when used with CYP2D6 inhibitors such as pridopidine) maintain positive benefits, and low dose ADMs can be used for treatment of chorea and behavioral disorders together with pridopidine.
CONCLUSION: The integrated analysis supports and validates PROOF-HD findings showing consistent, sustained, and clinically meaningful benefits of pridopidine in HD.

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Extraction and Introduction of HTT Protein Aggregates into *C. elegans* by Feeding

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BACKGROUND: *Caenorhabditis elegans (C. elegans)* is a valuable model due to its genetic tractability and observable nervous system. In this pilot study, *C. elegans* models (EAK 102 and EAK 103) expressing the Huntingtin protein were used to examine the role of Huntington's Disease (HD) protein aggregates in neurodegeneration and compared to N2 *C. elegans* wild isolate.
OBJECTIVE: This study aims to examine the effects of protein aggregates on synaptic transmission within *C. elegans*, and to model the effect that they may have on the human brain and in Huntington's Disease.
METHODS: A standard protein extraction protocol was utilized to extract the proteins from N2, EAK 102, and EAK 103 *C. elegans*, followed by feeding N2 *C. elegans* with the extracted proteins tagged with GFP. Finally the nematodes were imaged using a confocal microscope.
RESULTS: Visual examination of the confocal microscope images revealed protein accumulation primarily in the intestinal walls rather than the nervous system. Movement impairment was observed in fed EAK 102 and EAK 103 *C. elegans*.
CONCLUSION: The study suggests current methods may inefficiently deliver proteins to *C. elegans'* nervous system, as indicated by intestinal protein accumulation. Future modifications, such as prolonged exposure or lipid vesicle-mediated delivery, could enhance protein migration into the nervous system. Likewise, isolating protein aggregates using Tandem Affinity Purification (TAP) for subsequent analysis under native conditions could improve protein migration to the nervous system. Further experiments would include thrashing and aldicarb assays to assess synaptic transmission and overall nematode health following protein aggregate introduction.

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Exploring Place Of Death Among Individuals With Huntington's Disease In The US

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BACKGROUND: Despite the complex and personal nature of choosing a location for end-of-life care, little is known about where individuals with Huntington's disease (HD) in the US typically receive such care.
OBJECTIVE: To describe trends and identify factors associated with place of death among individuals with HD.
METHODS: Mortality data from the National Center for Health Statistics between 2009 and 2019 were used for this study. Place of death was categorized as long-term care (LTC) facility, home, hospital, hospice facility, and other locations. Trends in places of death were assessed using linear regression models. Multivariate logistic regression models were used to identify sociodemographic factors associated with place of death.
RESULTS: There were 13,350 individuals with HD who died in the United States between 2009 and 2019. The greatest proportion of deaths occurred in LTC facilities (48.4%) followed by at home (23.0%). A greater proportion of deaths in rural areas occurred in LTC facilities compared to all other locations ($p<0.001$ for all comparisons). In the multivariate model, age younger than 44 years, Black race, Hispanic ethnicity, some college education or greater, and being married were associated with significantly lower odds of dying in a LTC facility compared to home.
CONCLUSIONS: Despite a decreasing trend, LTC facilities remain a cornerstone of support for individuals with HD, particularly in rural areas. Additional studies are needed to further understand the impact of rurality and lack of support in the home on the accessibility and quality of LTC and end-of-life care for individuals with HD.

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Assessing Brain Bioenergetic Deficits in Pre-Motor-Manifest Huntington's Disease

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BACKGROUND: Huntington's Disease (HD) is characterized by metabolic dysfunction in the brain, but no studies to date have directly measured cerebral ATP in patients with HD. Quantifying bioenergetic brain deficits in patients with HD may propel development of novel disease modifying therapies for patients with HD.
OBJECTIVE: This pilot study aimed to quantify and compare cerebral ATP concentrations, a key metabolic indicator, between individuals with pre-motor-manifest HD (preHD) and healthy controls (HC) and explore the relationship between ATP concentrations, disease burden, and early clinical outcomes.
METHODS: We utilized non-localized, ultra-high-field 31-Phosphorous Magnetic Resonance Spectroscopy to quantify and compare cerebral ATP concentrations in nine preHD individuals and nine HC subjects. ANCOVA models adjusted for brain volume, age, sex, and BMI were employed. ATP concentrations were correlated with clinical measures of HD including the Unified Huntington's Disease Rating Scale (UHDRS®) Total Motor Score (TMS), Total Functional Capacity Score (TFC), Symbol Digit Modalities Test (SDMT), and years to predicted motor onset.
RESULTS: PreHD participants exhibited significantly lower concentrations of α, β, and δ ATP compared to HCs. Total ATP brain concentration decreased as subjects neared motor onset. Declining ATP concentrations were also associated with worsening TMS, TFC, and SDMT scores, suggesting a

direct link between reduced brain ATP and early clinical symptoms.
CONCLUSIONS: Our findings highlight the potential of 31P-MRS to serve as a direct assay for metabolic dysfunction in HD. Future therapies targeting metabolic deficits in HD may benefit from using direct measures of cerebral ATP concentration as markers of target engagement.

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Increased Neuronal Activity in Children and Young Adults with the HD Gene Mutation

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BACKGROUND: Huntington's Disease (HD) is linked to mutations in the HTT gene that lead to neurodegeneration later in life. However, HTT plays a key role in neurodevelopment, and emerging evidence suggests that CAG repeat expansions in HTT may confer developmental advantages early in life, such as larger cortical volume and higher cognitive scores.
OBJECTIVE: To determine if gene-expanded (GE) children and young adults have increased functional connectivity in the cortex relative to gene-non-expanded (GNE) children.
METHODS: This study analyzed resting state fMRI data from the Kids-HD study. We performed voxel-to-voxel global correlation analyses, agnostic of predefined brain networks, to compare cortical neural activity between the groups. We applied a family-wise error with a voxel-threshold of T>2.4 and a false discovery rate-corrected-cluster threshold of <0.05.
RESULTS: Our analysis revealed significantly heightened global correlation in several key cortical regions within the fronto-parietal network in GE subjects compared to GNE controls. These areas are associated with high cognitive functions and substantial bioenergetic demands.
CONCLUSIONS: The increased global correlation within the fronto-parietal network of GE subjects suggests a greater degree of neural synchronization and potentially higher metabolic expenditure in these regions. These findings may underscore the role of early neurodevelopmental changes in the pathophysiology of HD. The heightened global correlation in energetically demanding brain regions among GE individuals provides a novel insight into the bioenergetic costs associated with HD's neurodevelopmental advantages.

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Autonomic Dysfunction May Contribute to Disease Progression of Huntington's Disease

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BACKGROUND: Huntington Disease (HD) is characterized by chorea, cognitive deficits, and psychiatric symptoms due to striatal degeneration. Existing literature also points to autonomic nervous system (ANS) dysregulation in HD.
OBJECTIVE: Using Predict-HD and COHORT study data, we aimed to delineate the relationship between resting heart rate (rHR), clinical symptoms, and motor onset of HD.
METHODS: Subjects with available rHR data from the Predict-HD and COHORT studies were evaluated. We first investigated the relationship between rHR and clinical measures of HD (TMS, TFC, Stoop Test, SDMT, and cUHDRS®) using linear mixed effects regression analyses. We then evaluated only subjects with pre-manifest HD. These subjects were grouped into those with a mean rHR <70 bpm, 70-79 bpm, or ≥ 80 bpm. We performed a Cox Regression Survival Analysis to determine differences in the annualized risk of receiving a motor diagnosis between groups.
RESULTS: Amongst all HD subjects, there were significant relationships between all clinical variables and rHR such that higher rHR (worsening autonomic dysfunction) was associated with worse clinical outcomes (FDR<0.01). Furthermore, preHD

subjects with a mean rHR >80 bpm had a significantly higher annualized risk of receiving a motor diagnosis compared to subjects with a mean rHR <70 bpm (HR = 1.62, 95% CI [1.04 – 2.51], p=0.03). **CONCLUSIONS**: Our findings demonstrate that worsening autonomic dysfunction is significantly associated with clinical worsening of HD. Furthermore, the autonomic nervous system may serve as a target for future disease modifying therapies of HD.

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SPK-10001 AAV-Based MicroRNA Mediates Non-Allele Specific Reduction of *HTT* mRNA through RNA Interference, Demonstrating its Potential for Further Preclinical Development

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Reducing the amount of neurotoxic mutant huntingtin protein (mHTT) in neurons is expected to slow or halt progression of Huntington's disease (HD) in human patients when the therapy is initiated before neurodegeneration is advanced.

There are limited treatment options for HD. Although several drugs are specifically approved for treatment of chorea in HD patients (Tetrabenazine, Deutetrabenazine, and Valbenazine), there are no treatment options for worsening function or overall clinical disease progression of HD. Using gene therapy technologies, it is conceivable to provide a long-term effective therapy by anatomically targeting and lowering mHTT levels in the basal ganglia.

Spark Therapeutics is advancing the development of SPK-10001 gene therapy, designed to suppress the production of mHTT in HD patients. SPK-10001, an engineered adeno-associated virus (AAV), expresses an artificial microRNA (miRNA) targeting human *HTT* mRNA. Extensive testing of several miRNAs candidates, including those specific to exon 1, revealed that miRNAs targeting the 3'-OH terminal end of the *HTT* transcript resulted in the highest reduction of *HTT* mRNA. The lead miRNA was then selected from a pool of nine candidates based on consistent mRNA silencing levels, a safe off-target profile, and minimal to no disruption of the endogenous miRNA processing machinery *in vivo*.

SPK-10001 demonstrated a consistent, dose-dependent reduction of *HTT* mRNA and HTT protein, along with increased Darpp32 expression, when directly injected into the striatum of HD mice (YAC128 strain), compared to untreated controls. Subsequently, the comparable doses of SPK-10001 that were selected based on studies in mice were administered through a single intraparenchymal bilateral infusion into the caudate and putamen of non-human primates (NHPs). SPK-10001 induced a well-tolerated and stable reduction of up to 40% in *HTT* mRNA and up to 70% in HTT protein levels over twelve months period. In summary, the preliminary preclinical data showed no adverse effects associated with the reduction of *HTT* mRNA and protein levels and supports further preclinical development of SPK-10001.

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Route to a Safe Delivery Strategy for AAV-Based Gene Therapy to the Caudate and Putamen of Nonhuman Primates

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Adeno-associated virus (AAV) is a powerful and effective tool for delivering genetic medicines to the brain. AAVs can be administered to the brain by several routes (ROAs) including direct infusion to the brain parenchyma, via infusion into the cerebrospinal fluid (CSF) compartment (intraventricular, intra-

thecal, or intra-cisternal), or by crossing the blood-brain barrier after intravenous infusion.

SPK-10001 is a vectorized artificial microRNA which induces dose-dependent reduction in Huntingtin (HTT) mRNA and protein in vitro and in vivo, and which has potential for development as treatment for Huntington's disease. The microRNA is vectorized in a proprietary capsid that does not cross the blood-brain barrier efficiently after intravenous delivery. We therefore undertook a series of studies to determine safe and effective ROA for SPK-10001, with the goal of maximizing coverage of the brain regions (caudate and putamen nuclei) initially affected by Huntington's disease pathology.

We report here that only direct injection of SPK-10001 into brain parenchyma (IP) resulted in robust and consistent reduction in HTT protein throughout the caudate and putamen. None of the intra-CSF routes provided satisfactory distribution in the caudate and putamen. The combination of intra-CSF and IP injection of SPK-10001 did not further improve coverage of the target. However, in initial studies, IP delivery resulted in significant damage at the injection site that correlated with adverse neurological events. To address these issues, we optimized the surgical trajectories, infusion speed and rate, and the infusion volume. These modifications also improved consistency in coverage of the target brain regions and in levels of HTT protein reduction between individual animals. When we used the fully optimized surgical procedure, we were able to administer higher doses of SPK-10001 with minimal tissue disruption and limited microscopic changes (localized parenchymal, glial and inflammatory responses) concentrated at the injection sites. Optimization of surgical and infusion procedures is therefore an important step in the development of brain-directed gene therapies and may help ensure successful translation of those therapies to the clinic.

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SPK-10001 Induces a Durable and Safe Reduction of HTT Protein Supporting Further Development in Huntington's Disease

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SPK-10001 is a vectorized artificial miRNA that induces dose-dependent reduction in HTT mRNA and protein in vitro and in vivo and may have potential for further development in Huntington's disease.

We report here data from a pivotal animal study conducted to evaluate the safety of SPK-10001 in cynomolgus macaques. In this study, animals were injected with SPK-10001 via real-time intra-MRI bilateral infusions into the caudate and putamen nuclei of the brain using a SmartFlow® cannula (ClearPoint Neuro) and convection-enhanced delivery. Surgical trajectories (two per hemisphere) were planned in real-time using MRI and spread of the infusate was monitored throughout the procedure by use of gadolinium contrast agent. The surgical procedure was generally well tolerated with minimal pre/intra-operative immunosuppressive treatment.

Animals were maintained for either 3 or 12 months post dosing after which we evaluated biodistribution of the AAV and miRNA, levels of HTT mRNA and protein, and histopathological findings along with other safety-related endpoints. All doses were well tolerated, with no biologically consequential test article-related in-life observations or adverse histopathological changes observed at any dose tested. As reported in other studies in which therapeutics are administered via neurosurgical delivery, all animals in this study exhibited a transient elevation in neurofilament light chain (NfL) protein in cerebrospinal fluid (CSF) which returned to baseline by twelve months after administration of SPK-10001. NfL levels in the CSF of SPK-10001-treated animals did not differ significantly from sham surgery and diluent-injected controls, suggesting that the short-term elevation in NfL resulted from the surgical procedure and not the test article itself.

Finally, we report that levels of HTT suppression were stable over the 12-month analysis period and highly consistent among animals within a single dose group. These data demonstrate the safety of the surgical "infuse-as-you-go" convective delivery procedure and of infused SPK-10001. Overall, these data support the further development of SPK-10001 for Huntington's disease.

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Huntington's Disease Health Index (HD-HI) Correlations with Clinical Measures: An Analysis of KINECT®-HD Baseline Data

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BACKGROUND: The Huntington's Disease Health Index (HD-HI) is a validated, patient-reported outcome for evaluating disease-related burden in Huntington's disease (HD) [1]. The HD-HI includes 13 subscales and a total score. The first phase 3 study to implement the HD-HI was KINECT®-HD (NCT04102579), a 12-week trial of valbenazine for chorea in adults with HD [2].
OBJECTIVE: To correlate HD-HI scores with Unified Huntington's Disease Rating Scale (UHDRS®) measures using baseline data from KINECT-HD.
METHODS: Assessments included UHDRS measures of Total Motor Score (TMS) (higher=increased severity), Total Maximal Chorea (TMC) (higher=increased severity), and Total Functional Capacity (TFC) (lower=increased severity) and the HD-HI (higher=increased severity). Spearman rank correlations between baseline HD-HI and UHDRS scores were analyzed post hoc; correlation coefficients (r) are presented.
RESULTS: Correlations between HD-HI total score and UHDRS were highest with TFC (-0.42), followed by TMS (0.30) and TMC (0.17). HD-HI subscale correlations with TFC were highest with activity participation (-0.61), mobility (-0.50), social performance (-0.44), hand/arm function (-0.43), and communication (-0.35); the lowest was with pain (-0.17). HD-HI subscale correlations with TMS were highest with activity participation (0.43), hand/arm function (0.40), social performance (0.31), fatigue (0.25), and communication (0.23); the lowest correlation was with sleep/daytime sleepiness (0.11). HD-HI subscale correlations with TMC were highest with abnormal movements (0.27) and hand/arm function (0.22).
CONCLUSIONS: The correlations shown between the HD-HI and UHDRS indicate that individuals who have more severe motor symptoms and functional impairments also experience greater disease burden across multiple domains as measured by the HD-HI.

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Investigating the Link Between Cognitive Function and Structural Neuroimaging in Huntington's Disease

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BACKGROUND: Huntington's Disease (HD) is characterized by a pattern of brain atrophy, primarily affecting the caudate and putamen in the early stages of the disease [1]. Cognitive impairment is a defining feature of HD and may be associated with atrophy in specific brain regions.
OBJECTIVE: to explore the association between cognitive performance and brain structural measures in HD gene expansion carriers (HDGECs).
METHODS: 39 HDGECs (18 premanifest, 21 manifest) and 16 controls underwent a 3T brain MRI for volumetric assessment. The regions of interest (ROIs) were segmented using Freesurfer v5.3.0. Cognitive function was assessed using the symbol digit modality test (SDMT), verbal fluency test (VFT), and the Stroop interference test (SIT). Spearman correlation was employed to examine the relationship between the volumes of different ROIs and the scores of the cognitive tests.

RESULTS: Among HDGECs, the total volume of deep gray matter was significantly associated with SDMT, VFT, and SIT scores (rho=0.698, p<.001, rho=0.620, p<.001, and rho=0.506, p=0.005, respectively). The caudate, putamen, and globus pallidus showed the strongest correlations. Cortex volume also correlated with SDMT, VFT, and SIT (rho=0.580, p<0.001, rho=0.567, p=0.001, and rho=0.559, p=0.002, respectively). The frontal and occipital lobes exhibited the highest correlations, while the insula showed no significant correlation. In the control group, no significant correlations were found between the volume of different ROIs and cognitive test performance.
CONCLUSIONS: The volume of various brain regions correlates with cognitive function in HD patients. Future studies should investigate how longitudinal changes in brain volume relate to the progression of HD-related cognitive symptoms.

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Outcomes of an Expert Working Group to Choose Patient-Reported Outcome Measures for an Online HD Research Platform: POWERHD

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BACKGROUND: In 2023, HDSA partnered with the nonprofit organization Global Genes and its research platform RARE-X to launch a data collection initiative for the Huntington's Disease community called POWERHD. Now a collaboration between multiple advocacy groups, this IRB-approved research study collects data from affected patients, caregivers, and at-risk family members and provides that data on an open science research platform.
OBJECTIVE: The goal of POWERHD is to enable patients and families impacted by HD to participate in clinical research from home, reducing the barriers experienced by families without the means or the health to travel. Participants complete patient-reported outcome measures (PROs) to assess physical functioning, mental health, and impacts to quality of life and activities of daily living.
METHODS: To choose PROs for implementation on the POWERHD platform, two expert working groups were convened, each composed of 10-12 clinicians, patient advocates, and industry researchers. The first chose HD-specific measures and PROs addressing physical functioning. The second focused on PROs assessing cognition, anosognosia, anxiety, and depression. Each group met over approximately three months, reviewing, discussing, and ultimately choosing patient and caregiver-reported measures to maximize research impact but minimize family burden. The results of their expert consensus will be reported.
CONCLUSIONS: Patient and caregiver input is critical to inform drug development and regulatory decision-making, but that data must be robust, quantifiable, and available. Standardized COAs can be collected in collaboration with an inclusive, global community of HD patients, families, and advocacy groups to address equity barriers and support biomedical research.

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Altered Reward Responsiveness in Youth at Risk for Huntington Disease

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BACKGROUND: Alterations in reward responsiveness and risk-taking behavior have been identified as potential early markers of Huntington disease (HD) in premanifest gene carriers [1,2] but have not been investigated in youth at risk for HD. Reward positivity (RewP) is a neurophysiological measure of reward responsivity that has been associated with impulsivity [3,4] and can be modulated by stress and depression [5,6].
OBJECTIVE: To examine reward responsiveness using event-related potentials in youth ages 10-18 at risk for HD and to investigate the associations between RewP, psychological symptoms, and stress exposure.
METHODS: Twenty-nine youth at risk for HD (M_{age} 13.6, *SD* 3.1) and forty-six community controls (M_{age} 12.6, *SD* 12.2) completed a monetary reward task during continuous EEG recording. RewP was scored 250-350ms after feedback at Cz. Participants also completed the Youth Self Report (YSR) to measure affective symptoms and the Stress and Adversity Inventory (STRAIN).
RESULTS: Compared to controls, at-risk participants exhibited a blunted RewP to wins and no significant difference between win and loss conditions [$t(28) = 1.18$, $p = .25$)]. RewP amplitude did not correlate with affective symptoms in controls but was significantly correlated with aggressive behavior, externalizing problems, and total problems in at-risk individuals. After adjusting for age, sex, and income, RewP amplitude and total lifetime stress were significantly associated with externalizing problems in at-risk participants.
CONCLUSIONS: Youth at risk for HD show blunted responsiveness to reward, which correlates with externalizing problems and stress. Further investigation is needed to elucidate potential biological and environmental underpinnings of these findings.

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Developing RNA-Targeting Oral Small Molecules to Treat Repeat Expansion Disorders

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BACKGROUND: Genetic analysis has identified several genes including MSH3, PMS1, PMS2, MLH1 that repair as well as drive aberrant expansion of repeat sequences in the genome. These genes have been implicated in Huntington's disease (HD) and other neurological disorders including SCA1, DM1, FRAXA, and in vivo disease models provide evidence for a mechanistic role in driving somatic repeat expansion. We have developed a target and

lead discovery platform that enables the identification of orally bioavailable small molecules that predictably and selectively reduce the expression levels of target genes in a precise and tunable manner.
AIMS: We describe the identification, development and optimization of PMS1 RNA-targeting small molecules to modify the onset and progression of repeat expansion disorders (REDs) by targeting their root genetic cause, trinucleotide DNA instability.
METHODS/TECHNIQUES: CAG length of the Huntingtin gene was measured analytically and differences in somatic instability were quantified following chronic treatment of cells with PMS1 RNA-targeting small molecules.
RESULTS/OUTCOME: We demonstrate that reduction of PMS1 levels slows the expansion of CAG repeats over time both in artificial expansion systems as well as patient derived cells. A proof-of-concept effect was demonstrated in model systems of REDs with a reduction in levels of PMS1. Target engagement and a favorable pharmacokinetic profile was also achieved in monkeys in vivo with RGT compounds.
CONCLUSIONS: Our novel platform has enabled the identification and development of RNA-targeting small molecules that selectively target PMS1. Reduction of PMS1 levels slows the expansion of CAG repeats and reduces somatic instability in various models of Huntington's disease.

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Eye Movement Abnormalities in Early HD Affect Visual Information Gathering

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BACKGROUND: Oculomotor abnormalities are one of the earliest signs of HD, reported even in presymptomatic gene carriers (1). Saccadic eye movement abnormalities were previously investigated as an HD biomarker (2). Eye-tracking equipment has since become far easier to use. With free viewing tasks, the visual stimulus can be modified and measurement of eye blinks and pupil size taken.
OBJECTIVE: This study investigates eye movements in Huntington's Disease (HD) focusing on a novel free-viewing task including neutral and emotional faces.
METHODS: Ten individuals (3 men, 7 women), mean age 39 (range 26-67) yrs with early stage HD were recruited to the study. Eye movements were captured using the Eyelink 1000, which tracked saccades and pupillary responses. Individuals completed a dot-following task, to test voluntary and involuntary pro/anti-saccades, followed by free-viewing of a 20-minute video of 3-second clips including emotional faces, neutral stimuli and varied luminance. A matched healthy control group (n=24) was used for comparison.
RESULTS: T tests were used to compare prosaccade rates between groups. HD mean prosaccade rate (192.11 +/-26.37ms) was similar to healthy controls (195.63 +/-28.50ms), t(34)=0.36, p=0.72. HD anti-saccade rate (316.29 +/-123.94ms) was significantly slower than healthy controls (260.17 +/-43.36ms). During free-viewing, the HD group had greater central bias, made more saccades with shorter duration fixations, had greater pupil dilation with exaggerated pupillary response, blinking longer and more frequently than healthy controls.
CONCLUSIONS: Eye movement abnormalities in early HD suggest an alteration in how visual information is gathered from the environment is occurring.

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The Experience of Research Among Young People Impacted by Huntington's Disease

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BACKGROUND: HDYO is an international non-profit organization providing support, information and resources to young people impacted by HD. HDYO launched a series of surveys to better understand the global needs of young people.

AIMS: We present data from our second survey, exploring the experience of clinical research among young people impacted by HD.
METHODS: Participants provided informed consent prior to completing an anonymous, online questionnaire, available in six languages. Human research ethics approval was provided by Monash University.
RESULTS: Between January and May 2024, 112 eligible people responded to the survey. Respondents lived in Europe (42%), with further representation across North America (25%), South America (19%), Asia (6%) and Oceania (6%); 86% identified as female. Most respondents were gene-positive (47%), 18% were gene-negative, and 36% were gene-unknown.

When rating their knowledge of key research terms, many respondents had limited or no knowledge of commonly used terms such as open-label studies (58%), primary endpoints (68%) or safety monitoring committees (70%). Respondents had relatively better understanding of observational studies, interventional studies and placebos, however 32%, 39% and 36% of respondents respectively still rated having limited or no knowledge of these terms.

The most common barrier to participating in research was distance from a study site (18%) time away from work (14%) and anxiety about study procedures or side effects (11%). Financial assistance was the most frequently cited recommendation to increase participation.
CONCLUSIONS: Results of this survey are relevant to HD associations and industry partners seeking to engage young people in clinical research.

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Digital Health Technologies for Speech and Upper Limb Function Assessments in Huntington's Disease

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BACKGROUND: Current clinical assessments for Huntington's disease (HD) are limited in sensitivity and provide only a snapshot of patient disability. Digital health technologies (DHTs) offer a promising approach for frequent monitoring of disease severity and symptoms.
OBJECTIVE: To evaluate the use of wearable sensors and digital speech assessment in monitoring symptoms in HD.
METHODS: We recruited 18 individuals with manifest HD (mean age 49.9 ± 11 SD), 7 individuals with prodromal HD (mean age 34.6 ± 12.9), and 11 controls (mean age 55 ± 14 SD). BioDigit Speech was used to collect and analyze data during different speech tasks (e.g., counting forward). Participants also wore a PAMSys ULM wrist sensor for seven consecutive days on their dominant hand to monitor goal-directed movements during activities of daily living. Machine learning techniques were employed to classify HD, prodromal HD, and controls using speech and wearable-based measures. Regression analysis was used to predict clinical assessment scores (e.g UHDRS® motor, total functional capacity scores).
RESULTS: Classification based on wearable-based measures achieved a balanced accuracy of 67% and 0.72 recall for the HD group. Prediction of clinical scores ranged from 73% to 43%. Several speech measures were significantly different between HD and control groups, and showed similar potential for predicting clinical scores.
CONCLUSIONS: DHTs can track symptoms and disease severity in HD. The classification model performed well and regression analysis predicted clinical scores. These findings indicate that DHTs could enhance early detection and monitoring of HD and support further research to evaluate DHTs for use in clinical trials and care.

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How Early Does Anosognosia Begin in HD?

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BACKGROUND: Anosognosia, a lack of awareness of deficits, is common in individuals with

Huntington's disease (HD); however, exactly when anosognosia begins in HD remains unclear.
OBJECTIVE: To characterize the onset of anosognosia in HD by surveying its presence at various stages of disease using the HD Integrated Staging System (HD-ISS) and Total Functional Capacity (TFC).
METHODS: The Anosognosia Scale (AS), consisting of 8 items on which individuals rate their abilities relative to peers, was administered to 52 gene carriers, stratified by the HD-ISS and TFC, as well as their caregivers. Differences between caregiver and patient scores of ≥6 points corroborated the presence of anosognosia.
RESULTS: To our surprise, 30% of individuals in HD-ISS stage 0/1 (mean DCL=1.70); 29% in stage 2 (mean DCL=3.79); and 32% in stage 3 (mean DCL=4) showed anosognosia. Similarly, when stratified by TFC, 18% of subjects with a normal score of 13 (mean DCL=2.50); 38% with a TFC=10-12 (mean DCL=3.88); and 33% with a TFC ≤ 9 (mean DCL=4.0) showed anosognosia. Patients' lack of awareness of functional change appeared to occur earlier than their lack of awareness of cognitive difficulties.
CONCLUSIONS: We conclude that anosognosia appears early in the course of HD, even prior to manifest onset. This lack of awareness of deficits should dissuade against the use of self-report instruments as outcome measures in HD clinical research. Further studies will be needed to confirm and extend these findings.

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Using a Simple Body Sway Assessment Device to Track Balance Differences Across the HD-ISS Spectrum

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BACKGROUND: Huntington's Disease (HD) is a neurodegenerative disorder that typically emerges in the 4th/5th decades. Manifest HD diagnosis is largely based on motor onset. We have previously shown that balance impairment may begin early and serve as a biomarker of transition from premanifest (PM) to manifest HD. The HD-ISS is a new staging framework for assessing progression of HD for research purposes [1].
OBJECTIVES: To track onset and progression of balance impairment in HD using a simple body sway assessment and PIN HD-ISS Staging.
METHODS: Total body sway (TBS) was assessed in 161 gene-positive subjects using the BTrackS™ Balance Plate and laptop software. PIN HD-ISS was used to stratify these subjects into Stage 0/1 (n=74), Stage 2 (n=49), and Stage 3 (n=38). Four ten-second static balance trials with eyes open (EOC) and closed (ECC) were administered. Since data was not normally distributed, Kruskal-Wallis testing compared performance among cohorts.
RESULTS: Significant differences were found between Stages 0/1 vs Stage 3 and between Stage 2 vs Stage 3 (both p<.0001) in the EOC. Interestingly, in the ECC, statistically significant differences were also observed between Stages 0/1 vs Stage 2 (p=0.01).
CONCLUSIONS: Our findings indicate that a simple body sway assessment device is capable of tracking differences across the HD-ISS spectrum and that balance impairment likely begins prior to functional HD onset. Further studies will be needed to confirm and extend these findings.

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Examining Fall Risk in HD

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BACKGROUND: In Huntington's Disease (HD), balance impairment may begin prior to motor onset. As balance continues to deteriorate, HD subjects acquire even greater risk of falls.
OBJECTIVE: To examine fall risk in a well-characterized cohort of gene-positive individuals followed at one academic HD Center using a fall questionnaire and several established functional balance measures, including BtrackS™ Balance Device Total Body Sway (TBS), UHDRS® Total Motor (TMS) and Total Maximal Chorea (TMC) Score, Timed Up-and-Go (TUG), and 30 Second Chair Sit-and-Stand Test (CST).
METHODS: 157 gene-positive subjects were stratified into two cohorts based on their reported falls within the past year: Never N=139 [have never fallen] and Some N=18 [have fallen at least once]. Static balance trials with eyes open (EOC) and closed (ECC) on the BtrackS™ Balance Device, UHDRS TMS, TUG, and CST were administered to the participants.
RESULTS: Significant differences in TBS in both EOC ($p<.001$) and ECC ($p = 0.002$), with strong effect sizes of .942 and .846, respectively, were observed between the Never and Some Falls cohorts. Individuals with Some Falls showed significantly higher (worse) TMS and TMC scores (both $p<.001$) as compared to the Never Falls subjects. No significant differences were identified on the TUG or CST between the Never and Some Falls cohorts.
CONCLUSIONS: Our findings suggest that FR is more pronounced in individuals with worse TMS and TMC scores, in addition to those with greater TBS in both the EOC and ECC. Further studies will be needed to confirm and extend these findings.

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When Is a Book Club Not a Book Club? When It Is a Support Group!

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HD Reach

BACKGROUND: HD is a genetic, progressive, neurodegenerative illness with no current disease modifying treatment. Focus is on symptom management/supportive services. Many opportunities exist for in-person/online support groups. Group facilitators, however, report low turnout and/or "Zoom fatigue". HD Reach created a "Book Club" alternative to traditional support groups. This research examines attitudes and potential benefits of participants in monthly online Book Clubs.
METHODS: Through social media, and an organizational list-serve, people impacted by HD were recruited. The Book Club ran from May 2023 to July 2024. Participants were provided with a book series and met online one-hour monthly with a focus on the book content. The Book Club was facilitated by a social worker. After one year, participants were given a survey focusing on the Book Club's impact.
RESULTS: From May 2023-December 2023, average monthly attendance rate was 4.6. From January 2024-July 2024, average attendance rate was 9.14. Thirteen participants completed the survey. On a scale of 1=The Book Club Has No Impact on My Life to 5=Major Impact, all participants responded 4 or 5. Participants replied, "there was less pressure to provide personal information when the focus was on a book" and "taking the pressure off of being positive/negative was helpful since everyone could talk about the book at their own comfort level".
CONCLUSION: Support group participants can feel insecure, intimidated, or worry they will be overwhelmed by others. This Book Club concept allows people impacted by HD to focus on a "story" while at the same time forming community.

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Dysregulated Neuronal Maturation in a Panel of HD-Patient-iPSC Derived Striatal Neurons

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BACKGROUND: Although Huntington's disease (HD) is categorized as neurodegenerative disease evidence indicates that mutant Huntingtin disrupts neurodevelopment as well.
OBJECTIVE: To evaluate the neuronal maturation in human striatal neurons derived from HD patients iPSCs.

METHODS: Previously we established a human neuronal model by immortalizing and differentiating HD patient iPSCs into highly homogeneous immortalized striatal precursor neurons (ISPN), which recapitulated HD-like phenotypes of the parental iPSCs, including expression of MAP2/DARPP32 (Akimov et al, 2021). To further characterize this human HD striatal neuronal model, we investigated the neuronal maturation process in control (21Q,33Q) and HD (77Q, 109Q, 180Q) SPNs.
RESULTS: We found that HD ISPNs have more cells at the dividing phase than controls by cell cycle study, and their energy sources shift towards glycolysis by seahorse assays. Electro-physiologic analysis confirmed 180Q SPNs are functionally less mature than 33Q controls. To explore the pathways involved in maturation of the ISPNs, we compared the proteomics data of ISPNs before and after maturation. We found about 17% of proteins are dramatically up or down regulated by neuronal maturation in the control line. But 30-40% of these proteins are unchanged in 180Q upon differentiation. We identified SNAP91, a new synaptic marker, was dramatically decreased in matured HD ISPNs compared to controls. Isoxazole-9 can upregulate SNAP91, and promotes neuronal maturation in ISPNs.
CONCLUSIONS: Our data suggest that ISPNs derived from HD iPSCs appear to constitute a useful cellular model platform for studying neurodevelopment in human HD-patient derived striatal neurons.

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FDA Approved Compound Library Screening on Human Striatal Neurons Derived from iPSC in Huntington's Disease

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BACKGROUND: Huntington's disease (HD) is caused by a CAG repeat expansion in the huntingtin (*HTT*) gene, leading to pathogenic expansion of a polyglutamine tract in the huntingtin protein. No disease-modifying treatments for HD have been found to date and the recent failure of clinical trials of HTT-lowering approaches prompts the urgent need for identification of alternate pathogenic pathways and targets for novel therapeutics for disease modification.
OBJECTIVE: To screen disease modifying treatment in human striatal neurons derived from HD patient's iPSCs.
METHODS: Previously we established a human neuronal model by differentiating HD patient iPSCs into highly homogeneous immortalized striatal precursor neurons (ISPN), which recapitulated HD-like phenotypes of the parental iPSCs, including expression of MAP2/DARPP32 (Akimov et al, Hum Mol Genet. 2021 Nov 30;30(24): 2469-2487). Further, we developed a 96-well plate screening platform using CellTiter-Glo luminescent cell viability assay in the ISPNs and screened FDA approved compound library containing 817 compounds in HD ISPNs expressing 180 CAG repeats (180Q-SPNs).
RESULTS: We found that the compounds which protected HD ISPNs all belong to anti-inflammatory compounds category. The ongoing hits priority and validation studies will provide novel therapeutic targets for treating HD.
CONCLUSIONS: These findings suggest that targeting of neuronal inflammation may attenuate mutant HTT toxicity and provide novel therapeutic targets for developing neuroprotective HD treatments.

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A Proteomic Analysis of Huntington's Disease by Functional Capacity

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BACKGROUND: The molecular biology of Huntington's Disease (HD) has grown increasingly descriptive, with considerations for genetic modifiers, epigenetics, transcriptomics, the proteome, and the metabolome. Different levels of analysis offer opportunities to understand pathophysiological consequences of the altered huntingtin gene, and in turn potential therapeutic targets or predictive biological signatures.

OBJECTIVE: We previously examined the HD metabolome cross-sectionally in plasma and CSF for participants with varying degrees of functional impairment. Here, we describe the proteome in CSF from eight of these participants by their functional severity.
METHODS: TFC scores for participants were grouped for analysis as HD1/HD2 (7-13) or HD3/4 (3-6). Concentrations of proteins were also analyzed by individual TFC scores across the participant's entire range (3-13). Comparisons were exploratory and unadjusted for multiplicity; all p-values are nominal.
RESULTS: Of the metabolites assayed, 21 demonstrated nominal differences between earlier and later functional decline groups (nominal $p<0.05$). 5 of these decreased with worsening functional capacity (SCGN, CD70, ITGB6, GSTA1, TNFRSF8). The remaining 16 increased as TFC scores declined (CDKN1A, EREG, HAVCR1, TFRC, CA4, TNFAIP8, DEFB4A/B4B, IDS, IL-7, TMPRSS15, BCR, CCL5, IL-34, RAB37, VIM, ITGA6).
Across the full range of TFC scores, the strongest correlations among those showing increases with progression were for IDS (R^2=0.78), CA4 (R^2=0.77), CCL5 (R^2=0.76), and CDKN1A (R^2=0.62). For those that decreased with progression, the strongest correlations were seen for SCGN (R^2=0.77) and TNFRSF8 (R^2=0.67).
CONCLUSIONS: These data reveal new correlations between progression and regulators of inflammation, immune regulation, autophagy, oxidative stress, calcium homeostasis, DNA damage responses, the cell cycle, and apoptosis.

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Reducing Fraud in Web-Based Survey Studies in Huntington's Disease

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BACKGROUND: Web-based survey methods are commonly used in observational HD studies. Our team encountered fraud in a web-based HD survey study but found little published guidance regarding data integrity concerns in this population and internet setting.
OBJECTIVE: To describe the implementation of a fraud mitigation protocol in a web-based HD survey study and discuss data integrity considerations for future web-based research in HD.
METHODS: After beginning recruitment for a web-based survey study, it was noted that a large batch of fraudulent records (N=152) enrolled in a short span. In response, we consulted with the IRB to create a protocol for fraud detection. First, we attempted to contact first authors of manuscripts describing other HD survey studies. Then, feedback and recommendations from relevant reference publications were incorporated to create a thorough fraud reduction protocol.
RESULTS: Fraud reduction measures included modification of recruitment practices (e.g., removing recruitment materials from public, non-HD-specific websites and social media), addition of survey components to increase security (e.g., bot detection), and manually screening each new record using a detailed screening checklist.
CONCLUSIONS: It is difficult to avoid fraud in fully web-based studies in HD. In the study described, changes to recruitment methods, survey structure, and record screening procedures appear to have successfully limited fraud in the final sample, though these also required significant time resources and curtailed recruitment. Additional fraud-reduction methods exist (e.g., not offering compensation), but each of these has its own limitations. Investigators should consider incorporating formal fraud mitigation strategies in future web-based HD studies.

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Speech Outcomes Based on HDISS

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BACKGROUND: Clinical markers that show change in performance in people with Huntington's disease (HD) during the asymptomatic and prodromal stages remain a target of investigation in clinical medicine. Alongside genetic and neuroimaging initiatives, digital speech analytics has shown promise as a sensitive clinical marker of premanifest HD.
OBJECTIVE: To investigate the sensitivity of digital speech measures for detecting subtle cognitive-linguistic and fine motor features in people carrying the expanded HD gene, with and without symptoms.
METHODS: Speech data were acquired from 110 participants (55 people with the expanded HD gene including 24 asymptomatic HD; 11 prodromal HD; 12 early-stage HD; 8 mid-stage HD; and 55 healthy controls). Participants were grouped using the Huntington's Disease Integrated Staging System (HD-ISS). Objective digital speech measures were derived from speech tasks that fit along a continuum of motor and cognitive complexity. Acoustic features quantified speakers' articulatory agility, voice quality and speech-timing. Subjects also completed the single digit modality and the Purdue Pegboard bimanual task.
RESULTS: Some presymptomatic HD (furthest from disease onset) differed to healthy controls on timing measures derived from the syllable repetition and free monologue tasks. Prodromal HD presented with reduced articulatory agility, reduced speech rate and longer and variable pauses. Speech agility correlated with poorer performance on the upper limb motor test.
CONCLUSION: Tasks with a mix of cognitive and motor demands differentiated some prodromal and asymptomatic HD from the control sample after adjusting for age and sex. Motor speech tasks alone did not differentiate groups until participants were relatively closer to disease onset or symptomatic. Data demonstrated how ubiquitous behaviors like speech, when analyzed objectively, provide insight into disease related change.

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