Enroll!

Updates from the Enroll-HD global community

Contact us at info@enroll-hd.org

DECEMBER 2025

WELCOME TO *ENROLL!* 2025

Cristina Sampaio

Enroll! 2025 showcases the rapid progress being made in Huntington's disease (HD) research. We are excited to highlight the vital role of the Enroll-HD platform in providing critical resources for designing and conducting studies and trials, and to show how its data and biosamples continue to deepen our understanding of HD.

With more than 22,100 active participants at 157 sites across 23 countries, Enroll-HD continues to grow from strength to strength. To date, over 175 published papers have drawn on Enroll-HD datasets, and this momentum continued in September with the release of the seventh periodic dataset.

Enroll-HD 2.0 has been rigorously informed by recent scientific and therapeutic advances. Preparations for the transition to Enroll-HD 2.0 are well underway. They will ensure we are optimally positioned to address the modern realities of HD research and meet evolving regulatory requirements in the search for effective HD therapeutics.

We remain sincerely grateful to the individuals and families impacted by HD for their unwavering dedication to advancing clinical research.

Cristina Sampaio, MD, PhD
Chief Medical Officer, CHDI

Inaugural Huntington's Disease Clinical Research Congress 2025

The first HD Clinical Research Congress was held October 11–13, in Nashville, Tennessee, jointly organized by the Huntington Study Group and CHDI Foundation. The event attracted delegates primarily from North America, South America, and Australasia, who came from Enroll-HD sites in these regions, as well as industry representatives.

A selection of presentations is available on the Enroll-HD website: enroll-hd.org/2025-clinical-research-congress-video-gallery/.

The congress opened with a vibrant **HD Community Research Day** (October 11). It opened with a panel discussion aiming to demystify clinical research for participants and families, led by Arik Johnson (Huntington's Disease Society of America). Speakers included Daniel Claassen (Huntington Study Group), William Alexander (Alex) Dalrymple (University of Virginia), and Frances Saldana (HD-Care).

Next, Lisa Hale (Teva Pharmaceuticals) and Alex Dalrymple discussed the role of people with HD as partners in clinical research and decision-making surrounding participation. Danielle Buchanan and McKenzie Luxmore (both representing the Huntington Study Group) shed light on the informed consent process. Phyllis Foxforth (Huntington's Disease Society of America) presented on the FDA and ensuring that the family voice is heard. Katherine McDonell (Vanderbilt University Medical Center) and Danielle Buchanan elaborated on what study visits entail, reminding

us that research teams are in place to provide support and guidance. Victor Sung (University of Alabama at Birmingham) shared insights into the range of therapies currently under investigation for HD. After a participant panel discussion, the day was concluded with an 'ask the experts' Q&A session.

Merit Cudkowicz

The **Clinical Research Day** (October 12) opened with a keynote address by Merit Cudkowicz (Mass General Brigham Neuroscience Institute and Harvard Medical School) on progress in clinical development, in particular, flexible clinical trial design.

In a session dedicated to HD clinical trial updates, Victor Sung presented on uniQure's recent topline results for the AMT-130 gene therapy. Beth Borowsky (Novartis) shared updates on the oral huntingtin-lowering drug votoplam (PTC-518) and plans for a phase 3 trial in a larger group of participants early in the course of HD. Peter McColgan (Roche) provided an update on tominersen and other huntingtin-lowering approaches in development at Roche. Meghan Miller (Skyhawk Therapeutics) updated on SKY-0515, another oral huntingtin-lowering drug, and shared that the phase 2/3 FALCON-HD trial, currently running in Australia and New Zealand, will hopefully expand into additional countries.

In the progress in biomarker session, Hilary Wilkinson (CHDI) discussed the benefits of CAG-repeat instability as a biomarker for HD. David Hawellek (Roche) presented on the value of measuring mutant huntingtin and neurofilament light to inform decision-making in clinical trials, and introduced the upcoming HARMONISE: HD-NfL study. Killian Hett (Vanderbilt University Medical Center) shared insights into biomarkers found in spinal fluid and the implications for delivering potential therapeutics for HD. Jamie Adams (University of Rochester) highlighted how digital measures in HD can enhance trial design, monitoring, and care.

Jeff Long

The final session of the day focused on clinical research insights. Jeff Long (University of Iowa) argued for controlled clinical trials to confirm whether antidopaminergic drugs worsen the symptoms of HD. Stan Lazic (Prioris.ai) concluded with a consideration of how psychological symptoms such as depression and anxiety may impact the predictability of staging in the Huntington's Disease Integrated Staging System (HD-ISS).

Sam Frank

The Clinical Practice Day (October 13) started with a session on translational issues opened by Sarah Tabrizi (University College London). Sam Frank (Beth Israel Deaconess Medical Center and Harvard Medical School) considered how the HD-ISS, developed for research purposes, could also be used as a

Renowned speakers and enthusiastic delegates came together at the congress.

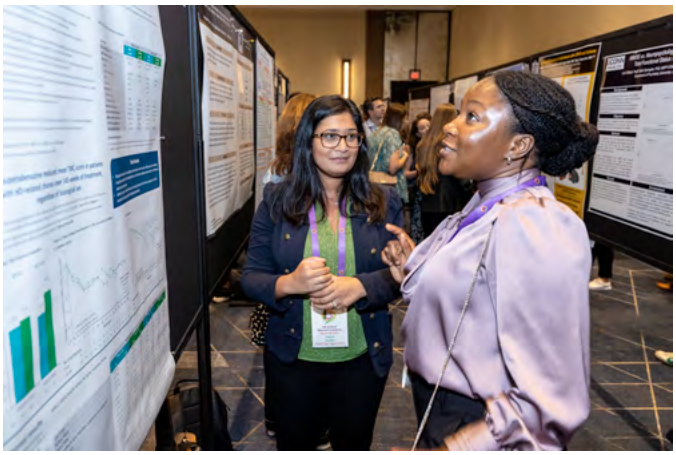
clinical tool. Dirk Keene (University of Washington) presented on efforts to modernize neuropathology in the study of Alzheimer's disease and moves toward application in HD. Joel Braunstein (C2N Diagnostics) shared reflections on the journey to developing the first highly accurate blood test for Alzheimer's disease diagnosis.

In 'Science for Clinicians: Hot Topics That Are Important to Communicate in Clinic', Davina Hensman-Moss (University College London Institute of Neurology) discussed therapeutically targeting somatic instability, the process by which repetitive DNA sequences, such as CAG repeats, lengthen within certain cells as a person ages. David Howland (CHDI) shared how potential therapeutics could simultaneously target mutant huntingtin and somatic instability.

Jeff Caroll (University of Washington) presented the HD Insights of the Year lecture, emphasizing that different approaches to lowering huntingtin have distinct effects and the implications for current clinical trials.

Erin Furr Stimming

The session dedicated to young people and HD was introduced by Erin Furr Stimming (UTHealth Houston Neurosciences). Bruce Compas (Vanderbilt University) delved into the emergence of cognitive symptoms in HD, drawing on a developmental approach to brain function. Cristina Sampaio (CHDI) then spoke on inclusion and exclusion criteria for clinical trials and the differing regulatory requirements in the U.S. and Europe. Martha Nance (Hennepin HealthCare HD Center of Excellence and Struthers Parkinson's Center) discussed aspects of clinical care in juvenile HD, reminding us that HD impacts the entire family.



Lively poster sessions created space for exchanges between presenters and delegates.

Finally, three short talks were selected for oral presentations from the poster submissions. Blair Leavitt (Incisive Genetics) discussed the company's lowering gene therapy, Christopher Mezias (Critical Path Institute) presented on frameworks for regulatory science and biomarker validation, and Jang-Ho Cha (Latus Bio) discussed targeting the DNA repair protein MSH3 to prevent CAG-repeat expansion.

Emily Gantman

Cristina Sampaio

Advancing Clinical Research: The HD Integrated Staging System

The HD-ISS provides a biological, evidence-based framework describing the progression of HD from birth through the end of life. CHDI's Chief Medical Officer, Cristina Sampaio, MD, PhD, and Vice President, Emily Gantman, PhD, explain the significance of the HD-ISS to the scientific community, emphasizing its value in providing a shared, common language for researchers.

Why was the HD-ISS developed?

Emily: We developed the HD-ISS with Sarah Tabrizi and colleagues, and this was published in 2022. It arose from the need to synthesize scientific advances in our understanding of HD by developing a conceptual framework to guide how we talk about and conduct clinical research in the field. In addition to the published paper, we recently created an infographic [see below] to explain the stages of HD in an accessible way.

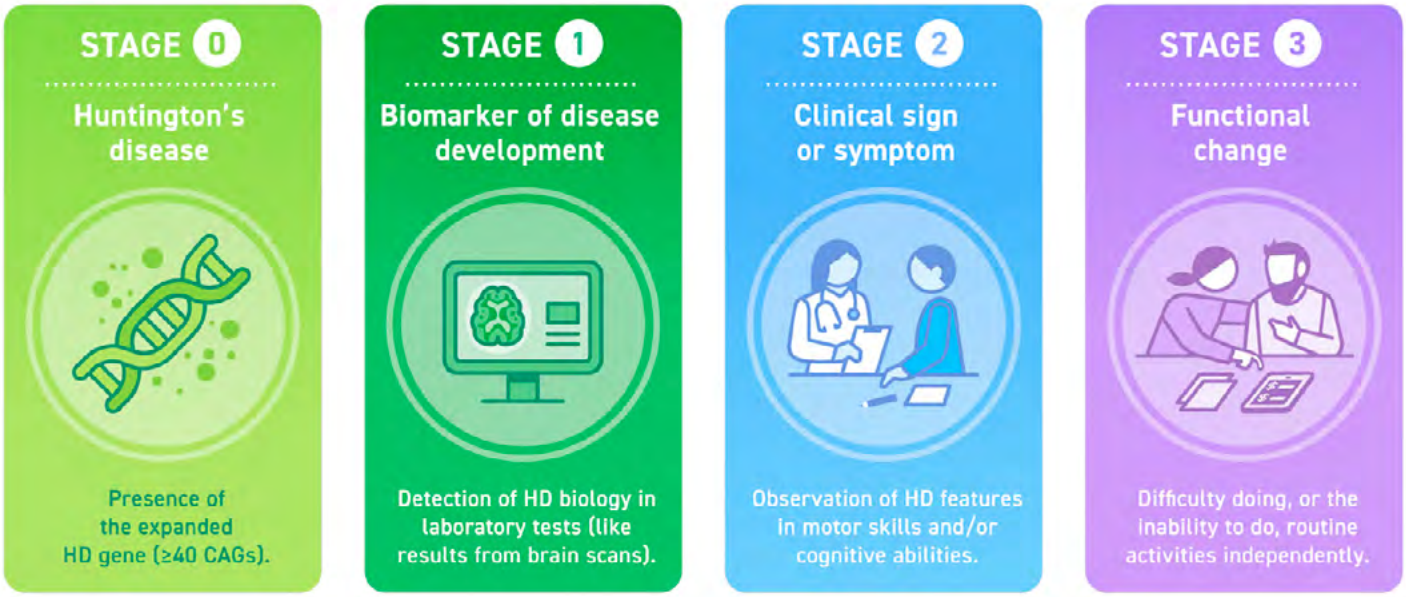
According to the HD-ISS, Stage 0 begins at birth and includes everyone with 40 or more CAG repeats who do not exhibit clinically relevant biomarkers, signs, symptoms, or functional changes associated with HD. In Stage 1, measurable changes in biomarkers of HD can be identified using MRI. In Stage 2, HD has progressed to the point where clinical signs and symptoms of HD are apparent on assessments such as the Unified Huntington's Disease Rating Scale Total Motor Score and the Symbol Digit Modalities Test. In Stage 3, the progression of HD is apparent through the loss of function or difficulty in performing daily tasks and activities independently.

Cristina: The substantial volume of data accumulated over the past two decades has yielded a far more detailed understanding of HD, including the unequivocal recognition that HD is present from birth. Since the discovery of the causative gene in 1993, genetic testing has enabled rapid and accurate identification of the mutation at any point in life, eliminating the need to wait for clinical symptoms to emerge for diagnosis.

In establishing the HD-ISS, we defined HD as the presence of a fully penetrant mutation – specifically, a CAG-repeat length of 40 or more. This represents a major shift from the previous reliance on clinical motor diagnosis, which is based on movement impairment, and typically occurs relatively late in the biological course of the disease, often in mid-life.

How does this approach align with the study of other diseases?

Cristina: Extensive research has shown that the structural brain changes associated with HD begin many years, often decades, before the appearance of any observable signs or symptoms, including those required for clinical motor diagnosis. The World Health Organization defines disease as any deviation from normal physiological or structural function, even in the absence of overt clinical manifestations. By this standard, HD constitutes a disease long before it becomes clinically apparent, and from a genetic standpoint, the causative mutation is present from conception. Together, these



HD Integrated Staging System (HD-ISS) overview. The HD-ISS is a staging system developed for clinical research, dividing the progression of HD into four distinct stages.

perspectives underscore the need to recognize HD as a lifelong condition rather than one that begins only at the appearance of clinically diagnosable symptoms. This is consistent with the U.S. Food and Drug Administration's broader perspective on neurodegenerative diseases, as demonstrated by its endorsement of similar approaches in developing treatments for conditions like Alzheimer's disease.

What are the advantages of the HD-ISS?

Cristina: As we've noted, HD has historically been defined by clinical motor diagnosis. When researchers wanted to study individuals before this point – spanning from birth to the presence of unequivocal HD signs and symptoms – inconsistent and interchangeable definitions such as 'pre-manifest', 'prodromal', and 'pre-symptomatic' were used. Adding to the confusion, 'early HD' has been used to refer to the period after motor diagnosis but before substantial functional impairment, which does not reflect the earliest stages of the disease. The HD-ISS addresses these ambiguities by providing clear, consistent terminology, enabling precise definition of disease stages, and supporting effective communication across HD research, including in clinical trials.

Emily: Just as the HD-ISS was developed based on current scientific understanding, it will continue to integrate future insights. While the stages themselves will remain unchanged to ensure continuity for researchers, a more detailed understanding of the stages' biology will evolve as advances in HD science unfold. For instance, as we gain a deeper understanding of biomarkers that define and differentiate the four HD-ISS stages, we will be able to layer these on top of the HD-ISS, enabling the formation of more precise cohorts for clinical trials and other research.

What are the implications of the HD-ISS for terminology?

Emily: Since the HD-ISS is based on a genetic definition of HD, the term 'gene carrier' is no longer appropriate. It is unhelpful to imply that disease processes are not already underway before symptoms become evident. Similarly, referring to an 'onset' of HD is misleading, because the disease is present from birth, a concept central to the HD-ISS framework. Instead, it is more accurate to describe individuals using the HD-ISS staging system: Stage 0 or 1 for periods when signs and symptoms are not readily apparent, and Stage 2 or 3 to indicate progression of symptomatic disease. For clarity, we should avoid using the word 'stage' unless we are specifically talking about the HD-ISS. And we should only use the word 'onset' to refer to the beginning of something specific, for example, 'the onset of clinical symptoms'. Where appropriate, to communicate the concepts previously referred to as 'before onset' or 'after onset', we recommend adopting before or after clinical motor diagnosis instead.

Much of the former terminology regarding HD progression can be mapped onto and used within the context of the HD-ISS. For example, clinical motor diagnosis typically occurs by the end of HD-ISS Stage 2. Additional existing terminology, such as that introduced by Shoulson and Fahn to describe disease severity, overlaps and remains very useful, particularly in the context of HD-ISS Stage 3. To be consistent with the HD-ISS and to describe what we previously called 'Shoulson and Fahn stage 4', we recommend using roman numerals in the context of the new system: HD-ISS 3-IV.

Cristina: The precise terminology introduced by the HD-ISS will be critical for advancing the HD field. As the HD-ISS now serves as the standard framework for classifying participants in observational and clinical research, consistent use of its terminology is essential – particularly to support regulatory alignment and decision-making.

Swati Sathe

An Update on Enroll-HD 2.0

Swati Sathe, MD, is Medical Vice President, Clinical Research, at CHDI. In 2024, she shared the 'why, what, and when' of Enroll-HD 2.0 with readers. We spoke with Swati to recap the key changes and hear the latest progress towards this exciting new chapter in HD research.

What is the purpose of Enroll-HD 2.0?

The Enroll-HD study is part of the Enroll-HD Platform. Enroll-HD 2.0 is an update to the original Enroll-HD study protocol. Key developments, in particular the HD-ISS and the emergence of potential therapeutic strategies targeting the root cause of the disease, underscored the importance of studying HD earlier in its course, necessitating change to the protocol.

What changes will Enroll-HD 2.0 introduce?

The updates to the protocol will primarily affect recruitment and assessments. Enroll-HD 2.0 will focus on maintaining a cohort of approximately 25,000 active participants. This target will ensure that the study remains manageable, maximize the effectiveness of the operational support provided by the Enroll-HD Platform, and enable the study to continue meeting its scientific objectives.

How will recruitment change?

Enroll-HD 2.0 aims to recruit younger participants to better understand the full spectrum of disease progression and to enroll participants with early disease processes that are currently under-represented in the study.

The HD-ISS framework is integral to Enroll-HD 2.0. All participants, new and existing, will be assigned to a study cohort: Cohort A, Cohort B, Cohort C, or Control. Cohorts are broadly aligned with the HD-ISS stages, with Cohort A including participants up to 44 years of age and typically representing HD-ISS stages 0 and 1. Cohort B will include participants aged 45 years and older, typically representing HD-ISS 2–early 3. Cohort C will include participants with more advanced disease progression, that is, HD-ISS 3. Transition to Cohort C will be based on clinical characteristics rather than age.

How will assessments change?

An important feature of Enroll-HD 2.0 is that the study will evolve with participants and ensure that assessments are appropriately tailored to each person's cohort assignment. Following careful scientific review and input, a selection of new and modified assessments has been included in Enroll-HD 2.0, while several assessments from the previous protocol have been removed. These revisions enable the

maximum utility of the collected data while keeping the testing burden manageable for participants.

What are substudies?

Enroll-HD 2.0 introduces the additional category of substudies to the Enroll-HD Platform. A substudy is a type of nested study in that it utilizes data already obtained through Enroll-HD, but has additional requirements. Two key substudies may be available to Enroll-HD participants: iEnroll, which will collect additional imaging data, and Origin-HD, which will collect semen from male participants.

What other developments are in the pipeline?

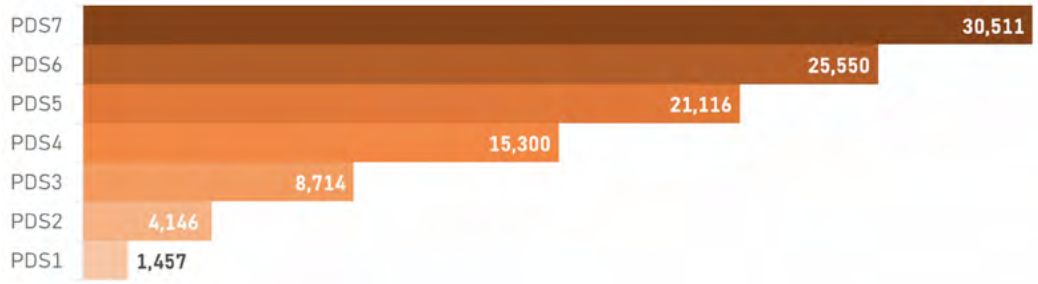
Alongside Enroll-HD 2.0, a new biobanking framework will enable CHDI to store and distribute vital data as well as receive and store biosamples. The Enroll-HD Collaborative Biobank will establish a standardized, clearly defined process for receiving, storing, and sharing biological samples and data from people with HD and control participants. This initiative aims to accelerate the development of biomarkers in HD research, allow further investigation into the genetic and environmental factors that affect HD pathophysiology, and inform the development of disease progression models and clinical assessment tools in HD and other neurodegenerative conditions.

When will these changes take place?

Preparations for making the transition to Enroll-HD 2.0 are well underway. The operational infrastructure is undergoing significant modifications to support the new features included in the amended study. Work is currently in progress to develop new and revised study procedures where needed, as well as other necessary resources, such as training materials for site teams, an electronic data capture system, and language translations.

A critical aspect of the transition is developing a carefully considered country- and site-level rollout plan. This rollout will be executed in phases and will take several years. There is a lot of work to be done, but we are steadily making progress toward Enroll-HD 2.0.

Jen Ware



Enroll-HD sample size by PDS release.

Enroll-HD Datasets: A Key Resource for HD Researchers

The Enroll-HD platform provides researchers with access to high-quality clinical datasets and biosamples to accelerate HD research and development. We spoke with Jennifer Ware, PhD, Director of Experimental Design at CHDI, to learn more about the available datasets and their impact.

Why does the Enroll-HD platform offer clinical datasets?

To fuel HD research! The Enroll-HD platform is designed as a resource 'hub' for HD researchers – and in line with this philosophy, we serve as a no-cost 'one stop shop' for clinical datasets and biosamples from a multitude of HD studies. In addition to Enroll-HD's periodic and specified datasets, the platform offers researchers access to clinical datasets from other HD studies, including HDClarity, TRACK-HD and Track-On HD, PREDICT-HD, REGISTRY, IMAGE-HD, HD-YAS, and more.

Tell us about the latest Enroll-HD data release – PDS7!

The seventh Enroll-HD periodic dataset was made

available this September. PDS7 contains data from 30,511 Enroll-HD study participants, and encompasses 112,992 study visits, making it the largest HD cohort dataset available to researchers. The PDS7 overview document provides a synopsis of the dataset, sample size, visits, and the sociodemographic and clinical characteristics of the cohort.

Excitingly, PDS7 includes approximately 1,000 participants with RNA samples, following the collection of the first sample under this initiative in February 2024. We are eager to see how data and samples from these participants will be used! Another highlight of this release is that it contains data from nearly 1,000 participants who have had *10 or more* Enroll-HD study visits. This longitudinal coverage is invaluable to many researchers, and it truly speaks to the dedication of Enroll-HD study participants.

Enroll-HD periodic datasets provide HD researchers access to high-quality, longitudinal data across a broad range of assessments from an extremely large cohort. These attributes, in combination, provide a valuable opportunity for researchers.

How are the datasets being used?

The HD research community has responded enthusiastically to Enroll-HD – we have received *hundreds* of requests for Enroll-HD data and biosamples from researchers all over the world. When researchers request access to these resources, we ask them to provide a short description of their planned project, and we post these descriptions on our website. The intention of this is two-fold: to encourage collaborative research and, critically, to inform research participants about how their data and biosamples are used. **I encourage you to browse through these projects and see what's underway!**

Enroll-HD was designed to support clinical trials, enhance our understanding of HD, and improve clinical care. The data and biosamples Enroll-HD participants have provided have allowed our research community to do exactly that.

We've seen companies leverage Enroll-HD data for clinical trials (e.g., uniQure), and researchers have used Enroll-HD data in developing the HD-ISS, advancing biomarker research, developing assays to measure the huntingtin protein, informing an HD phenotype atlas, and identifying several genetic modifiers of HD milestones – critically pointing to new targets for which therapeutics are now being developed. In terms of clinical care, Enroll-HD data have provided important insights into suicidal behaviors, and the effect of modifiable environmental factors on disease progression.

We track and highlight all publications leveraging Enroll-HD data, biosamples, and infrastructure – 175 so far and counting.

Enroll-HD datasets have demonstrably contributed to our greater understanding of HD. Importantly, none of this would be possible without the continued dedication and commitment of HD families and the Enroll-HD study site staff. Thank you!

Arun Karpur

Applications of Enroll-HD Data in Clinical Research

Arun Karpur, MD, MPH, is a physician-scientist and epidemiologist with over 20 years of experience in driving clinical, public health, and public policy research, who joined CHDI in 2025 as Director, Clinical Statistics. We were keen to hear about how Enroll-HD data have been used in key developments.

How did Enroll-HD data contribute to the development of the HD-ISS?

The HD-ISS was developed with input from prominent HD researchers and clinical professionals, who used Enroll-HD data to confirm its feasibility and utility for describing disease progression. The richness and consistency of Enroll-HD's clinical and biosample data demonstrated that clinical progression can be segmented into four stages, enabling precise determination of progression at the individual level.

What is the descriptive phenotypic atlas, and how did Enroll-HD data contribute to it?

The descriptive phenotypic atlas was published by Douglas Langbehn and colleagues in 2023. It summarizes the range and distribution of HD phenotypes – or traits – associated with HD, including motor, cognitive, psychiatric, and functional features across various CAG-repeat lengths, ages, and functional levels. Additionally, an online compendium of summary values of different clinical markers of disease progression was created to equip practitioners and researchers with data to improve their understanding of disease progression and support clinical decision-making.

For instance, by entering values for a given CAG length, a practitioner can explore the average distribution of scores according to age for the Total Motor Score component of the Unified Huntington's Disease Rating Scale. From this, they can gain insight into the individual patient's rate of progression compared to that typically observed among the HD population participating in the Enroll-HD study. These insights can inform what additional tests and assessments would be useful to ensure effective monitoring and support. This is a useful tool for patients and their caregivers as well as physicians, and can be found at enroll-hd.org/for-researchers/atlas-of-hd-phenotype.

How was the standardized CAP score developed, and why is it useful to HD researchers?

CAP score is a CAG-Age-Product, calculated by multiplying an individual's CAG-repeat length in the huntingtin gene by their age. A higher CAP score suggests greater cumulative exposure to the toxic effects of the mutant huntingtin protein and more advanced HD progression. Unfortunately, small but important differences in how this has been calculated make it difficult to compare between studies. The standardized CAP score published by John Warner and colleagues in 2022 addresses this limitation by providing a common benchmark for comparing different studies and aiding clinical trial design through more accurate recruitment and stratification.

How have Enroll-HD data been used directly in clinical trials?

Enroll-HD data has been used in multiple ways. First, Enroll-HD data have been used as an external comparator arm in clinical trials. For instance, uniQure's recent AMT-130 phase 1/2 study used a matched comparison group drawn from the Enroll-HD data, reporting substantial slowing of disease progression. Also, given the quality and longer duration of data collection, sponsors are using Enroll-HD data as an additional comparison to sham or placebo groups.

Second, Enroll-HD data are used by many sponsors to support planning for clinical studies, determine clinically meaningful study endpoints, calculate the number of participants needed, and develop optimized study designs and approaches.

Finally, Enroll-HD data have been used as real-world evidence. In the GENERATION HD1 study, Enroll-HD data were compared with the control arm to demonstrate long-term placebo effects in the 'sham' group. Understanding placebo effects in HD is critical because they can mask disease progression and interfere with the evaluation of experimental therapeutics.

How do you envision Enroll-HD data being used in the future?

Enroll-HD is a crucial platform that provides real-world evidence data on the clinical progression of HD. The revised and updated protocol will collect even more pertinent and targeted clinical and biomarker information, including data on important genetic markers. This information will deepen our understanding of HD progression and the factors that contribute to overall patient experiences. Most importantly, Enroll-HD data have the potential to inform drug discovery that can delay or even halt disease progression in the early stages of HD.

uniQure's AMT-130: Current Status and Next Steps

AMT-130 is an experimental gene therapy that delivers a tiny piece of genetic material into the brain. This genetic material tells brain cells to make a small RNA molecule that lowers levels of both normal and mutant huntingtin. The therapy is delivered directly into the striatum using a modified, harmless virus (AAV5) that serves as a delivery vehicle in this one-time surgical procedure.

On September 24, uniQure announced promising topline results for their phase 1/2 study of AMT-130 in HD. The high dose of AMT-130 met the study's primary endpoint by demonstrating statistically significant slowing of disease progression (as assessed by the composite Unified Huntington's Disease Rating Scale) at 36 months compared to a propensity score-matched external control (Enroll-HD natural history data). The high dose of AMT-130 also demonstrated statistically significant slowing of disease progression as measured by Total Functional Capacity at 36 months compared to a propensity score-matched external control. There were 12 participants in the high-dose and low-dose groups, and AMT-130 was generally well-tolerated with a manageable safety profile.

uniQure announced on November 3 that discussions with the FDA indicated that external control data would unlikely serve as the primary basis for AMT-130 Biologics License Application. This was confirmed on December 4 in a further press release from uniQure.

uniQure anticipates further discussions with the FDA in early 2026. The study is currently ongoing, and the HD community looks forward to the scientific publication of the full results, as well as additional data as the study progresses.

Amy Brown, Spencer Diehl, and Katherine McDonell with team members

Engaging Families, Empowering Research

Amy Brown, MD, MS, Assistant Professor of Neurology, Spencer Diehl, LCSW, Social Worker, and Katherine McDonell, MD, MSCI, Assistant Professor of Neurology, are integral members of the dedicated and dynamic Huntington's Disease Program at Vanderbilt University Medical Center, USA. We spoke with them to learn more about their important work and their focus on engaging families in HD research.

How did you get involved in Enroll-HD?

Amy: I've been involved in HD research at Vanderbilt as a movement disorder specialist for about six years. I now serve as co-director of our Huntington's Disease Center of Excellence and as a principal investigator for Enroll-HD and HD-Clarity. I stepped into these roles following Daniel Claassen, who built our outstanding Vanderbilt program and set the foundation for its continued success.

Katherine: I've been here for about 11 years, having first come as a fellow in 2014 when the clinic was just being established. From the beginning, I was especially drawn to working with young people impacted by HD and became involved in providing genetic counseling and support for those considering testing. My work with these young individuals and their families has shaped many of my clinical and research interests.

Spencer: I joined Vanderbilt's Center of Excellence in 2021, coming from a community mental health background. In speaking with Daniel, I realized how much overlap there was between my previous work and the challenges faced by people with HD – particularly around psychiatric symptoms and concerns about disease progression. I undertook a crash course in HD and quickly fell in love with the community and this patient-centered multidisciplinary team.

Tell us about Vanderbilt's multidisciplinary approach.

Katherine: We run a dedicated full-day clinic once a week where physicians, a nurse practitioner, multiple social workers, and a speech therapist see patients. Our genetic counselor is also on site several times each month. Providing timely care is a priority, and we strive to schedule all new patients within 4 to 8 weeks of their first contact with us. We're also working to add physical therapy and occupational therapy expertise to our team. Many people travel long distances to receive care here, and we want to offer each individual the most comprehensive clinical support possible.

How else do you support people with HD?

Amy: We are focused on addressing the needs of each individual, but also the entire family. Our social work team excels at reaching out to patients before their visits to understand their priorities and how best to support them. Another key element of our approach is the range of research opportunities we offer, including Enroll-HD. Because our clinical care naturally involves the whole family, we're well-positioned to support patients interested in participating in research. Getting to know families early – and allowing them to get to know us – helps make the transition into research far less daunting, even for young adults. In fact, we've found that while some young adults may prefer not to be seen in clinic, many are still eager to take part in Enroll-HD.

Katherine: As we worked toward providing truly family-centered care, we recognized a significant gap in services for children in families affected by HD. To address this, we partnered with a child psychologist at Vanderbilt who brings extensive expertise in childhood stress and coping to our multidisciplinary HD team. Together, we developed a research program recruiting parents with HD and their children, ages 6 to 30. This work allows us to explore family dynamics, communication, and social isolation, and to consider how best to support young people, including those who are too young to undergo genetic testing.

How do you sustain community engagement?

Spencer: We stay connected with families through events like our annual education day and a variety of activities throughout the year, including monthly educational video calls. Recently, for example, a neuropsychologist gave a presentation on modifiable risk factors for brain health. This area consistently draws strong interest from people eager to learn how they can support their well-being across the lifespan.

We also see renewed engagement when external developments occur, such as the recent positive topline results from the uniQure trial, which prompted many individuals we hadn't heard from in some time to reach out. While not everyone can participate in the uniQure trial, there remains strong enthusiasm for contributing to research, and Enroll-HD provides an accessible and meaningful way for people to get involved.

What does Enroll-HD 2.0 offer young people?

Amy: A major draw for young people is the opportunity to contribute to the broader HD community. On an individual level, participating in Enroll-HD allows them to stay connected to the clinic without needing to receive clinical care until they're ready. It also provides a pathway to learn about their eligibility for additional studies, such as HDClarity.

Katherine: We also know from the broader field of neurodegenerative disease research that, to achieve meaningful therapeutic impact, interventions need to begin as early as possible. Likewise, we need a deeper understanding of which cognitive and behavioral measures are most sensitive to disease progression across different ages. For example, impulse control may warrant closer attention and more precise assessment tools. Enroll-HD 2.0 provides a tremendous opportunity to explore these questions and to build a much clearer picture of the earliest cognitive and behavioral changes associated with HD.

Connecting Norway to the Global HD Community

As Norway's only active Enroll-HD site, Oslo University Hospital has become an important touchpoint for families impacted by HD. We spoke with Lasse Pihlstrøm, MD, PhD, leader of the Huntington's Disease and Neurodegenerative Genomics Group and Enroll-HD principal investigator, about what Enroll-HD means for the HD community in Norway.

The Oslo Enroll-HD team, from left: Nora Raaf, Solveig Jacobsen Dalbro, Ellen Hoven Maurtveten, Marleen van Walsem, and Lasse Pihlstrøm. Team members Ahmad Kaddoura and Sjur Prestsæter were absent when the photo was taken. Credit: Åsne Rambøl Hillestad, UiO

How did you get involved in Enroll-HD?

Our site previously participated in REGISTRY, and when I arrived, one of my first tasks was to complete the ethics paperwork and help establish Enroll-HD. Fast forward to today, and we now have around 100 patients regularly attending our clinic, many of whom are in the early stages of HD. Alongside providing multidisciplinary clinical care, we also offer opportunities to take part in Enroll-HD and other research studies. These opportunities are eagerly taken up, particularly by our younger patients.

Why have so many younger participants become involved?

We have close links with the Department of Medical Genetics at Oslo University Hospital, as well as the other university clinics involved in diagnostics for rare and inherited diseases across Norway. The team responsible for predictive genetic testing builds strong relationships with patients over a series of appointments during this critical period and routinely shares information about Enroll-HD. As a result, we receive many referrals through this pathway.

Another important referral pathway is the Norwegian Association for Huntington's disease, which provides online information, meetings, and webinars, creating different opportunities for us to engage with the HD community and provide information about Enroll-HD. They've had some amazing ambassadors who've spoken openly about their experiences being part of Enroll-HD and shared that it's a really beneficial experience.

Why is Enroll-HD so important?

Enroll-HD is a global effort, and being part of it means a great deal to many within the HD community. Participants appreciate the chance to come in once a year, meet with professionals, and discuss any concerns they may have. For younger adults in particular, these annual visits can be very reassuring, and they give us the opportunity to build a supportive network well before any signs or symptoms of HD appear. We always encourage the participants to bring family members to visits, and they are often eager to get involved too.

Many participants also appreciate the chance to contribute to disease-modifying therapy trials. Enroll-HD plays a key role in this by providing high-quality observational data, as highlighted by the recent uniQure topline results. Participants understand that being in the database does not guarantee involvement in industry-sponsored trials,

but it does increase the likelihood of being considered for such opportunities.

Our ambition is to stay closely connected with the international research community and to make our site an attractive and visible partner for industry sponsors, as well as for potential international academic trials. We share the common goal of advancing disease-modifying therapies for HD, and although Norway is a small country, being part of Enroll-HD reminds us of the progress being made –and the important role we can all play in that effort

HDID: Linking Participant Data Across Studies

Rebecca Fuller, PhD, is Vice President, Clinical Outcomes, at CHDI and an expert in cognitive research with people with movement disorders and psychiatric illness. Her recent work includes the development of a new initiative for participants in Enroll-HD about their HDID. We spoke with Rebecca to find out about the benefits for participants and researchers.

Rebecca Fuller

What is HDID?

The HD identification number, or HDID, is a unique nine-digit ID assigned to each participant in the Enroll-HD study. It is generated once using a secure algorithm, and the same number stays with the participant throughout their Enroll-HD journey. The HDID is linked to the data collected at each annual visit, but it is never connected to personal information such as name or address. The HDID is extremely useful for both Enroll-HD participants and researchers.

Why is HDID important?

We use HDID to link participant data across studies, including Enroll-HD data. So, if a participant takes part in another study or clinical trial, such as an online study or a pop-up study, they don't have to repeat the same tests. Thanks to the tremendous commitment of Enroll-HD participants, we already have a rich and extensive dataset. HDID enhances the value of this resource by enabling researchers to easily connect it with data from smaller, short-term studies they conduct.

Tell us more about pop-up studies!

We launched pop-up studies several years ago to collect data at events such as the Huntington's Disease Society of America annual convention. During these events, we invite delegates to take part by visiting our stand or a dedicated space, depending on the venue layout. In recent years, these pop-up studies have helped us gather data to support the development of novel digital measures, such as gait assessments, as well as other important pilot and questionnaire data. Participation is quick and convenient, making pop-up studies an easy way for people to contribute to research. With HDID, we can now seamlessly link data collected through a pop-up study or survey to a participant's Enroll-HD data.

How do participants get their HDID?

At present, the best way to obtain an HDID is to contact your study site, where the personnel can provide it upon request. We are also developing new web and mobile applications that will enable participants to generate and securely store their own HDID in the future.

What are the implications for research beyond HD?

We are committed to embracing new technologies, and through this process we're gaining fresh insights into how we can deepen our understanding of HD. Many of these insights may also benefit research into other rare diseases where innovative methods are essential to fully maximise the value of the data contributed by each individual.

You can find out more about online studies on the Enroll-HD website: enroll-hd.org/for-hd-families/current-studies-online/.

Jenna Heilman and Matthew Ellison, HDYO founder

Young Voices, Big Impact

The Huntington's Disease Youth Organization (HDYO) aims to support, educate, and empower young people impacted by HD. Executive Director Jenna Heilman works tirelessly to ensure these goals are met. We caught up with Jenna to discuss recent developments and the central role of young people in HDYO's activities.

How has HDYO developed in recent years?

When we emerged from the COVID-19 pandemic, we were multinational but not as international as we wanted to be. In becoming an umbrella organization that helps bring young people into the HD community, we've linked up with national and local associations in each country to provide much-needed collaborative support to individuals. We've been able to show how HDYO can be helpful to local associations, and also how local associations can partner with HDYO.

Developing these connections is already paying off, and we've seen that many young people are keen to get further involved in leadership roles and our ambassador program. Our ambassadors are young global leaders who volunteer, support each other, raise awareness, and fundraise for HDYO. We now have more than 120 ambassadors from 32 different countries. As our ambassadors interact with people, they refer more young people to us.

Community is really important, and too often we hear of young people who had previously felt there was no one to reach out to. In addition to in-person events and support groups, we have a large community of individuals connected on WhatsApp. For young people, social media and instant messaging are crucial avenues of support, and we are continually developing our provision.

We've also been working on online educational resources, such as 'Breaking Down Barriers' and other content available on our YouTube channel, and exploring ways to make these resources even more relevant and useful to the community. We recognize that in HD, numerous stigmas, challenges, and fears are associated with sharing one's story, so we've explored ways to enable individuals to contribute anonymously, by using avatars, for example. There's a huge value in empowering underserved communities with people who talk and look like them – and avatars can provide a way to achieve this.

The observational studies dating game at the 2025 congress

What sort of in-person activities does HDYO offer?

In 2023 we had our first in-person congress in Glasgow, and in March 2025, this took place in Prague, attended by more than 370 young people, with around 90 to 95% retention to the very last session. We unveiled our research terminology, which continues to grow and is now being translated. Our observational studies dating game was a great hit,

and overall, the congress really set the scene for our work going forward.

Alongside these larger meetings, we also run HD camps, which allow us to provide support within small groups. We match up HD professionals, typically social workers, with two to three young volunteers who have lived experience, in a camp group of no more than seven young people. It's all set up around the specific needs of each group, which may involve exploring issues such as genetic testing or grief and loss, for example. The critical focus is on making the content relevant and meaningful within the safety of a small group. While camps are currently based in North America, we are now looking at ways to build relationships with local support systems to expand the format of the program further afield.

How are young people involved in the design of these activities?

Every new program we create undergoes a vetting process with our ambassadors, and these insights are really powerful. After events, such as congresses, we obtain feedback from ambassadors and participants through debriefs and surveys, and ask questions about what worked and what didn't. Even when we're thinking about logos and merchandise, ambassadors are at the forefront of our decision-making process. For the past few years we've been running a series of surveys to better understand different aspects of our community's lives as they continue their journey with HD. Speaking with our ambassadors means that we can ask the right questions.

What can Enroll-HD 2.0 offer young people?

Enroll-HD 2.0 has the potential to give young people a really important seat at the table for research, particularly when we're thinking about biomarkers and understanding the early progression of the disease. Of course, age and disease progression often go hand in hand, and we all want to see an interventional therapy that can keep HD at bay for as long as possible while ensuring the maximum level of quality of life. Enroll-HD 2.0 has the potential to really steer that.

For young people to feel empowered and motivated to participate in research, we need to provide them with support and education. We've already had great discussions about how we can collaborate with professional communities to support young people and ensure that Enroll-HD 2.0 is as successful as possible. It's really exciting to have this open dialogue, and we will continue to champion collaboration.

HDYO provides a comprehensive range of resources for children, young people, families, friends, and professionals. Find out more here: hdyo.org.
YouTube: youtube.com/hdyofeed
Twitter: @HDYOFeed
Facebook: facebook.com/HDYouthOrg
Instagram: instagram.com/hdyofeed

EHDN Clinical Research Congress 2026

The EHDN Clinical Research Congress will take place in Krakow, Poland, October 22–24, 2026.

Hoa Nguyen

Nayana Lahiri

The Programme Committee, chaired by Hoa Nguyen (Ruhr University Bochum) and Nayana Lahiri (St George's University Hospital London) of the EHDN Executive Committee, notes that the event will build on the success of the 2024 EHDN & Enroll-HD meeting in Strasbourg and further expand the integration of the clinical development programme. As in previous years, the biennial

meeting will feature the EHDN Business Meeting, a strong focus on ongoing and upcoming clinical trials, and presentations on cutting-edge scientific advances. A particular highlight of the 2026 congress will be a keynote lecture by Nobel Laureate Aaron Ciechanover, a renowned expert on the role of the ubiquitin system in HD and other neurodegenerative disorders. Further details, including the programme and registration information, will be available in early 2026.

Robi Blumenstein

And Finally...

We conclude our 2025 issue of *Enroll!* with reflections from Robi Blumenstein, President of CHDI.

This has been a significant year for the HD community.

In February, the 20th Annual HD Therapeutics Conference in Palm Springs, California, set the stage for the busy and inspiring year to come. Fast forward to October, the inaugural HD Clinical Research Congress organized by the Huntington Study Group and CHDI proved to be a tremendous success. Looking ahead to 2026, we eagerly anticipate the 21st Annual HD Therapeutics Conference in February and the EHDN Clinical Research Congress in Krakow, Poland, in October.

Therapeutic progress brings cautious optimism to the pursuit of disease-modifying treatments for HD. uniQure's topline results for AMT-130 described above, for the first time suggest that lowering mutant huntingtin in people confers a real clinical benefit; an important biological proof of principle. Yet much work still lies ahead. As highlighted throughout this issue of *Enroll!*, the Enroll-HD platform continues to play a vital and unique role in advancing scientific, clinical, and therapeutic research.

Every step forward in our understanding of HD has been made possible by the dedication of individuals and families impacted by the disease, as well as clinicians, researchers, and professionals working in the field. As 2026 approaches, the strength of the HD community and the value of unity are clearer than ever.

Enroll! is a publication of CHDI Foundation, Inc., a nonprofit biomedical research organization that is exclusively dedicated to collaboratively developing therapeutics that will substantially benefit those affected by Huntington's disease. As part of that mission, CHDI Foundation sponsors and manages Enroll-HD. More information can be found at: www.chdifoundation.org

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