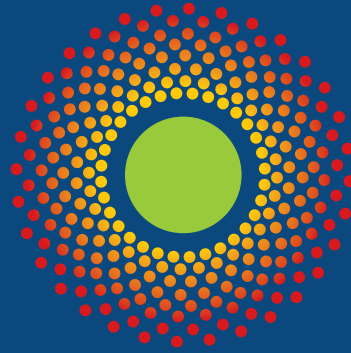


Enroll!

Updates from the Enroll-HD
global community



10-YEAR ANNIVERSARY SPECIAL ISSUE

AUTUMN 2022

ENROLL-HD: 10 YEARS STRONG

This special issue of *Enroll!* celebrates the 10-year anniversary of Enroll-HD, the large global community it now represents—almost 28,000 participants at 155 sites in 23 countries on 4 continents—and the achievements it enables that are fueling Huntington’s disease research. Building on the foundational work of the preceding REGISTRY (Europe) and COHORT (North America) studies, Enroll-HD has set the standard for natural history studies in rare diseases and become an invaluable and trusted clinical research platform for the HD community.

Enroll-HD has transformed the landscape of HD clinical research and drug development, and the last 10 years have been filled with many successes and firsts in the HD field, some of which are highlighted in this issue. Of course there have also been challenges and disappointments—that is the frustrating nature of drug development—but as a community we continue to push forward, learning, adapting, and growing towards the ultimate goal of delivering therapeutics that will substantially improve the lives of those affected by HD. Thanks to your commitment and dedication, Enroll-HD has made great strides toward achieving its three major aims:

Support clinical trials Almost half of all participants in current or recently completed HD clinical trials also participate in Enroll-HD, and Enroll-HD sites have made up almost 90% of the clinical sites involved in these trials.

Enhance the understanding of HD The wealth of data and biosamples contributed by participants has led to exciting scientific breakthroughs, including the development of new classification systems for disease staging in research, advances in biomarker research, the development of assays to measure the huntingtin protein, and the identification of several genetic modifiers of disease onset that point towards important new therapeutic targets.

Improve clinical care Clinical care has been improved by encouraging regular clinic visits, using standardized assessments, training clinicians, and fostering a culture of excellence.



These and all the other accomplishments we will highlight throughout the coming year are only possible because of the dedication, commitment, and hard work of the health-care professionals, advocates, researchers, sponsors, donors, and, most importantly, the HD families who contribute their data and biosamples to Enroll-HD. Each of you has made an active choice to contribute your time, energy, and knowledge.

In this special anniversary edition of *Enroll!* we spoke with just a few of the thousands of people who have helped make Enroll-HD what it is today. These voices—some new, some familiar—describe what Enroll-HD means to them, how it has affected their lives by creating connection and hope, and how it has enabled innovative HD research. We sincerely hope you are proud of what you have accomplished.

Anne Rosser PhD FRCP is professor of clinical neuroscience at Cardiff University, UK, and chair of the European Huntington's Disease Network. She has been involved with Enroll-HD from the very beginning and is the lead neurologist for the Enroll-HD clinical site that covers the whole of south Wales.

How do you think Enroll-HD has affected the care that individuals with HD receive?

On a global level, we've learned a lot more about the HD phenotype [the clinical characteristics and presentation of the disease]. We now have a large connected group of neurologists, psychiatrists, psychologists, and other healthcare professionals who now tend to share their ideas more readily in terms of what they find works and what doesn't, and I think that's been really valuable for care.

Enroll-HD ensures a systematic way of collecting data. When you use the same measure for every individual you see, it's much easier to follow someone and understand how they are progressing clinically.

What aspects of Enroll-HD stand out regarding research, and how has that enabled further research?

Enroll-HD is massive from lots of points of view! There are very few diseases where such large numbers of participants have been followed over such a long period of time, along with biosamples. You can see the value of this when you consider what the GeM-HD consortium has achieved in identifying genetic modifiers of age of motor-symptom onset (see Jim Gusella interview). While we don't yet have effective treatments, really interesting targets have been identified that I think will yield treatments in time.



Anne Rosser – cheers!

Having such a huge dataset that researchers can mine in terms of hypothesis generation – being able to ask a question and interrogate the existing data – provides a sound basis for future research and applying for supporting grants. That's pretty amazing! Colleagues working on different diseases are often quite jealous that we have this huge longitudinal study. And it's kept on developing with studies such as HDClarity and imageClarity, for example.

Another value of Enroll-HD is that having many clinical sites experienced in HD up and running has been fundamental to being able to conduct interventional trials, such as those carried out recently by Roche. And having a huge database from which individuals can be invited to take part in further studies is a real benefit – these are people that we know because we see them at least once a year, which means we build up a trust and an eagerness to be involved as a community. The HD community is very open to helping further understanding of the disease.

“There have been massive changes... now we are looking at exciting potential therapeutic targets that we knew nothing about 10 years ago”

How do you think the HD research landscape has changed over the past 10 years or so?

Ten to fifteen years ago, we didn't know very much about HD in terms of the pathology or phenotype, and we didn't have any disease-modifying clinical trials at all. Enroll-HD was only just starting and since then the landscape has changed out of sight. If I think back to the presentations I was doing back then it is clear that all of that work has moved on a lot. There have been massive changes, particularly in the genetic modifier work, because we just didn't have enough participants to run those sorts of studies. Now we are looking at exciting potential therapeutic targets that we knew nothing about 10 years ago, and that is very much due to Enroll-HD. Enroll-HD took what was happening with its predecessor, REGISTRY, and moved it to a whole new level, and in doing so became the catalyst for the remarkable progress we've made.



21,044 ⁺
Current Participants

What's the most inspiring incident that you've encountered through Enroll-HD?

Well, this isn't a single inspiring incident but I always find the number of patients who come and give their time, even when they're having a really difficult time themselves, really quite amazing. I've had participants who were just recovering from cancer treatment and others coming in

only a few weeks after losing close family members. This puts it all into perspective. As someone involved from the start, the enthusiasm from the Enroll-HD team is also really inspiring and has kept the whole project really alive and vibrant. Ten years on, Enroll-HD is still going with no signs of dissipating – a remarkable accomplishment for the whole community!

Daniel Claassen MD MS is professor of neurology at Vanderbilt University Medical Center and director of the Vanderbilt Huntington's Disease Center of Excellence in Nashville, Tennessee, where he is principal investigator at a large Enroll-HD clinical site.

Tell us about your clinical site and how Enroll-HD plays a role.

We started as an Enroll-HD site about eight years ago and now have more than 400 participants. Enroll-HD has given us the opportunity to build the clinic and also our research and education work. The benefits are multifaceted – without Enroll-HD we wouldn't be able to support our research nurses and social workers, for example. And for participants, Enroll-HD offers the opportunity to engage in the broader study of HD globally – that involvement resonates with our patients and families, and they want to be a part of it!

How has Enroll-HD supported research?

To start with, there's the funding that's supported the infrastructure, plus the availability of huge amountsof data from Enroll-HD that can better guide decision-making when we're trying to tackle very difficult issues like "how big is the sample I need?", and "what's the endpoint I should look at, and how does that variable change over time?".

"Enroll-HD has given us the opportunity to build the clinic, and also our research and education work"



Daniel Claassen (second from left) and the rest of the Vanderbilt Enroll-HD team

There's also the patient engagement that results from having Enroll-HD and knowing that we're going to see someone regularly – on a yearly basis. This normalizes discussions about research, and for participants provides a context in which to understand research and the associated trade-offs and benefits of taking part.

How has being part of Enroll-HD helped improve care?

Often, when someone with HD sees a neurologist, the main interest is in the motor symptoms and there may be a lack of attention to mood or cognitive issues. Enroll-HD assessments force us to comprehensively and systematically assess the full range of symptoms in our clinic and we can see the benefits of this in our clinical care.

One outcome is that we have developed a really close relationship with our psychiatry team and referrals for in-patient psychiatry because we saw a lot of people who were depressed and suicidal. I think our care improved because we had the opportunity to reflect on what we were assessing and the results from these assessments. This holistic, patient-centric view is central to Enroll-HD because sites are required to take account of every aspect of a participant's health. It made us see how we needed to broaden our clinical scope.

catch up every year. This sort of communication is really important.

“This holistic, patient-centric view is central to Enroll-HD because sites are required to take account of every aspect of a participant's health”

How do you think the HD research landscape has changed over the past 10 years and what role has Enroll-HD played?

A lot of the outcome measures we now use more generally in clinical care and research are based on Enroll-HD. There's certainly been an acceleration in clinical trials that we wouldn't have otherwise seen and we're fortunate that so many companies are invested in this.

One reason for this is that we have a better understanding of the disease trajectory and where interventions [therapeutics] may or may not fit in. If you're a pharma company and you're able to get advice from a foundation like CHDI that has followed nearly 28,000 research participants over time to allow you to understand how things change and how quickly, especially in a rare disease, then this is an invaluable resource. Because of Enroll-HD, we're now asking questions about what happens earlier on in the disease and, critically, whether we can intervene earlier.



155+

Clinical Sites

What aspects of Enroll-HD strike you as being key to its success?

First of all, there is the clinical applicability of the measures that we give participants. As a result of this, HD researchers know how things change over time, what things are important, how they can be measured, and participants can see how this impacts their clinical care. Second, there is the routine and the sense of staying connected with the clinic – even if there may not be much going on for a participant, we still

ENROLL-HD WEBSITE - UPDATED!

We launched an updated version of the Enroll-HD website at the start of this year with improved functionality, new content and features, with a modern look and feel. A resource for the whole HD community – including families, advocates, clinicians, researchers, and anyone else who has a connection to or an interest in HD – the homepage quickly navigates the user to the most relevant sections tailored for specific audiences.

For HD Families can help you learn more about the Enroll-HD study and platform and how it all works, clinical research opportunities and how to get involved, and better understand HD and the research into developing novel therapeutics. And the new comprehensive Resources page for each of the 23 countries that are currently part of Enroll-HD, compiled with input from local HD advocacy organizations, now lists local support networks.

Over the coming year, we will be expanding the website to incorporate content relevant for clinical trial sponsors, study sites, and governance committees, as well as translating the For HD Families pages into multiple languages.

As always, we appreciate any feedback and ideas on how to further improve.

Saül Martinez-Horta PhD is a neuropsychologist and researcher at the Movement Disorders Unit at Hospital de la Santa Creu i Sant Pau in Barcelona. Having previously worked as an EHDN language area coordinator as part of REGISTRY, Saul has been involved with Enroll-HD since its inception.

What does being involved in Enroll-HD mean to you?

Being involved in Enroll-HD from the beginning has allowed me to contribute to the preparation of a world-wide project that has gone far beyond the original idea of developing a multidisciplinary clinic for HD! This is particularly clear in terms of the research resources that Enroll-HD offers.

How has Enroll-HD facilitated research?

I am convinced that, as a platform and a scientific structure, Enroll-HD has played a central role in how the scientific study of HD has evolved globally. This extends far beyond what we are doing at our site. The worldwide perspective and developments in clinical trials and research that we now have are amazing, and there is a clear association between Enroll-HD and these developments.

Enroll-HD

is not just an observational study – it provides structure and cohesion

to the field. Multicenter studies such as Enroll-HD allow us to collect a tremendous amount of data that help us in the understanding of HD, and participants are aware that they are part of something really big.

In terms of the practical aspects, at a site like ours identifying potential participants who can be invited into clinical trials can now be determined with a few clicks at a computer. Of course, recruitment into clinical trials needs to be fast and effective, and Enroll-HD ensures this need is met!

Do you think Enroll-HD has contributed to improving care?

The assessments that we conduct, and the follow-ups with individuals and their families, all mean that we spend much more time working directly with individuals. I remember when my grandfather visited the neurologist about 15 years ago and it was like, ‘OK, you have Huntington’s. See you

“Enroll-HD has played a central role in how the scientific study of HD has evolved globally”

“In terms of taking care of people, this feels unique”



Saül Martinez-Horta with his son, Saül

later, in two years or whatever.’ This has changed completely. With Enroll-HD, people know that they will come to the clinic for visits on a regular basis and be offered the opportunity to participate in other things. In terms of taking care of people, this feels unique.

What’s your favourite thing about working in Enroll HD?

There are many things but for me, one really important thing is working with HD families. This is amazing not just from a professional perspective but from a human perspective. You are facing people living with a devastating condition

and it’s such an amazing thing to understand and see how they deal with this kind of experience. This

goes far beyond the medical aspects, it’s more existential than that. The kind of lessons I learn every single day, working in the HD field is amazing. I used to tell my students that to understand the clinical perspective, you need to just listen to people and listen to what they explain about how they are living.

45,990⁺

Biosample Vials Used

G. Bernhard Landwehrmeyer MD PhD FRCP is professor of neurology at Ulm University in Germany, where he also directs the Huntington Disease Center. With a long history of working in HD, Bernhard is one of the founding members of the EHDN and is the principal investigator of Enroll-HD.



G. Bernhard Landwehrmeyer

How do you think the clinical research landscape has changed in the 30 years you've been working in HD?

To my mind, the biggest change over the past 30 years – and this is at least in part due to Enroll-HD – is a strong spirit of collaboration, a desire of HD clinical sites to work together across the globe and to cooperate in multicenter studies, building on an emergent global community of HD families, clinicians, and researchers.

The original concept behind Enroll-HD was to combine existing natural history observational studies to create a global platform that incorporated North America, Europe, Australia, New Zealand, and also some countries in Latin America and Asia. It was becoming increasingly apparent that future clinical interventions and randomized controlled trials would be global exercises, and that a community of study sites dedicated to HD providing a more unified, more harmonized platform would be appropriate for this task. Of course, HD is a global problem and Enroll-HD is yet to become a fully global platform, but this remains an important aspiration.

 **61 M⁺**
Data Points

My perception is that the research landscape and the care community over this time period have grown together, because we all are aware that we are working on a joint program, using a shared platform across many countries, and all contributing to one project, Enroll-HD. Each and every contribution of clinical data and biosamples contributes to enhancing our knowledge and understanding of HD, and this is yielding very, very important insights.

What factors do you think have been important in the success of Enroll-HD to date?

I think the trust developed between all the relevant parties—families, researchers, clinicians, and other healthcare professionals—has been critical. For example, trust has been built between the clinical sites and the families affected by HD, who can rely on the sites to both provide excellent care and also offer research opportunities. When trust is in the room, good things happen. And this is what we see with Enroll-HD.

The funding that Enroll-HD provides to the clinical sites has brought many benefits, including allowing the employment and retention of experienced and skilled staff, as well as investment in their ongoing training and development. This continuity is important, it

means we can ensure both high-quality assessment processes that ensure the accuracy of data collected and that the experience is a positive one for participants.

Another factor is the openness with which we share data. All the clinical sites and researchers are aware that

“When trust is in the room, good things happen. And this is what we see with Enroll-HD”

conclusive studies in rare diseases require a sufficient number of observations, and this cannot be achieved as a standalone effort. Enroll-HD enables research

to be informed by appropriate numbers of participants and it is understood to be a unique collaboration in which individuals’ contributions to the greater whole are fully acknowledged.

I believe that partners in the pharmaceutical industry appreciate very much how well organized the HD community is and appreciate the value of Enroll-HD in recruitment, the knowledge obtained on site, and the worldwide capabilities. It’s a no-brainer really – thanks to Enroll-HD, there is no need for feasibility studies by outside partners as the Enroll-HD operational team is sufficiently knowledgeable already.

We almost exclusively do conclusive trials – by that, I mean trials that are suitably powered to answer the question we are asking. While the answer that we get may not always be to our liking, this is why we do clinical trials in the first place. Enroll-HD has made a major contribution to the improved understanding of biomarkers and their place in clinical development, as well as supporting clinical research more generally.

What about the next 10 years? What do you see on the horizon for Enroll-HD?

I'd like to see more research on the biomarkers, endpoints, and outcome assessments we use in HD clinical research, and I think

Enroll-HD is the perfect platform to speed up their development and validation in the next 10 years. But most importantly I hope to see Enroll-HD deliver on the hope that, with global collaboration and the expedited validation of appropriate assessment tools and endpoints, we will succeed in correctly identifying the potential of novel chemical entities or other new interventions. We can

“One of the truly inspiring things... is the generosity and the mindset of families participating in Enroll-HD”

never know for sure whether the interventions that we are exploring in clinical trials will hold up to the high hopes that we place in them – positive outcomes are not guaranteed. But what we can guarantee is that by improving the efficiency of the processes in which we generate evidence, we can come to solid, robust clinical trial results that we can rely on.

Finally, what is the most inspiring thing you've encountered working with Enroll-HD?

One of the truly inspiring things that I have experienced multiple times first-hand is the generosity and the mindset of families participating in Enroll-HD. That mindset is “I'm not doing it

for myself, I'm doing it for a better future for my children and other people affected within the HD community”. And this is a mindset in which the first question is not “what is in it for me?” but “what is in it for the community?” For me, this is the most inspiring thing about Enroll-HD and I believe the right mindset with which to contribute to research and, ultimately, overcome this devastating disease.

Greg Witkowski MD PhD—principal investigator at the Enroll-HD site at the Institute of Psychiatry and Neurology in Warsaw—and **Danuta Lis**—president of Polskie Stowarzyszenie Choroby Huntingtona, the main HD advocacy organization in Poland—speak about how Enroll-HD has affected clinical care, research, and the experiences of HD families in Poland.



Greg Witkowski

What does being part of Enroll-HD mean to you and HD families in Poland?

Greg: We are thrilled to be on board with Enroll-HD for many reasons, including the benefits it brings to care. Enroll-HD visits are much longer than routine outpatient visits for people with HD, and the assessments are conducted in a much more systematic and detailed way. As part of Enroll-HD we assess motor symptoms,

psychiatric status, and also cognitive abilities to gain a fuller understanding of each individual, and these assessments are repeated every year. This means that individuals and their families know where they are in terms of disease progression and what they can expect in the future.



Danuta Lis

As many as 99% of the people who come into our clinic are also part of Enroll-HD, and many started as far back as 2014, meaning we have data for the past eight years, which is really valuable. I think that we also manage participants' clinical care more effectively because they have been assessed multimodally. We don't just know about an individual's clinical status but also their specific circumstances regarding caregivers and

social situations. This allows us to respond more effectively to each individual's needs, determine whether their existing help is appropriate and sufficient, and refer them for further support if needed. In my opinion, Enroll-HD has made the day-to-day work of clinicians much more effective.

Danuta: I've been representing HD families in Poland since 2005 and have seen significant changes. One positive change is participation in Enroll-HD, with many people involved from the very beginning—it is a chance to participate in something important that will benefit them and their children, and knowing that they are part of the large group of HD families and professionals who are looking for a cure for HD gives them hope. I participate in meetings with the Ministry of Health in committees for patients with rare diseases, and I know that many rare diseases do not have the information base of Enroll-HD and so nothing progresses.

What else do you think Enroll-HD offers families?

Danuta: Enroll-HD offers families an important opportunity to meet with professionals and clinicians and talk about their experiences, ask questions, discuss the future, and also talk about the stigma they may feel. There is an increase in openness and acceptance as a result of taking part in the research, and also an increased sense of community through Enroll-HD. When I talk to individuals and families, I hear that they feel much stronger and more informed in terms of the disease than they did before Enroll-HD.

Greg: At the clinic we have also seen an increase in openness. It is really important for families to be aware that they are taking part in something that isn't just based at one site or one hospital, but that they are part of a project that is taking place all over the world. I think participants feel less alone through taking part in Enroll-HD because it is such a huge study and it provides a sense of community. I frequently hear participants talk about feeling hopeless in the face of having a terrible disease but Enroll-HD helps reduce this hopelessness. The education component of Enroll-HD is also worthy of mention because it opens up important conversations

“Thanks to Enroll-HD, HD families in Poland can trust that there is a very good reason for hope!”

“I think participants feel less alone through taking part in Enroll-HD because... it provides a sense of community”

and people exchange information both within and across families.

How do you think Enroll-HD has facilitated clinical research more generally?

Greg: The very large majority of our participants are also involved in different projects and trials relating to HD, including DOMINO-HD, a large European multicenter project on digital biomarkers. International cooperation in research is very important and in Poland we are conducting research that is absolutely dependent on Enroll-HD. Having quick and effective access to the huge Enroll-HD database of very well-characterized individuals is the perfect tool for maximizing research efforts, and this attracts pharmaceutical companies interested in HD to Poland to conduct their research. Much less research would be happening in Poland if it were not for Enroll-HD.

In general, I think people are very keen to be part of the exploration in furthering our understanding of HD. There are other diseases, such as Parkinson's disease, where, sadly, the sorts of opportunities offered by Enroll-HD just aren't available.

How do you think the HD landscape has changed over the past 10 years?

Greg: I started working in HD research in 2007 and we mostly had very small studies conducted at different institutions with small numbers of participants. This has changed completely because now we have large multinational, multisite studies, including Enroll-HD and clinical trials. Because we have built up infrastructure and technical capabilities at our site, we can recruit more participants and organize this all much more effectively. Enroll-HD has made huge contributions to all of this.

Danuta: The landscape has changed a lot in the last 10 years. We know much more about the disease and, thanks to Enroll-HD, HD families in Poland can trust that there is a very good reason for hope!



Louise Vetter with her family

Louise Vetter is president and chief executive officer of the Huntington’s Disease Society of America (HDSA). Enroll-HD is the only research endeavor ever to be formally endorsed by the HDSA.

What was it about Enroll-HD that led to its endorsement by the HDSA?

The idea of a global platform in HD research really compelled the HDSA Board of Trustees to look at Enroll-HD as something different. Enroll-HD was not just a study, it was not just a research initiative, it was a truly novel global initiative to accelerate not only therapeutic development but also, potentially, the trajectory of more meaningful care. Together, these elements made it very easy for HDSA to say that Enroll-HD deserves our full support. The fact that Enroll-HD was not just for folks at a certain stage of the disease, but that it was for anyone in an HD-affected family, presented a completely different invitation for community participation compared to what else was available at that time, and that, I think, was very powerful and inspiring.

How do you think Enroll-HD has changed the clinical research landscape since that time?

Thinking back, the clinical research landscape for HD was actually quite segmented and fractured 10 to 12 years ago. While there were several different observational and clinical studies taking place, the clinical science and work going on with different industry partners were not as sophisticated as we see today.

“Enroll-HD has normalized how we think about participating in clinical science – and that is huge”

What is revolutionary about Enroll-HD, as it was conceived and continues to be, is that it is very much a uniting force. Enroll-HD has helped bring families together – globally – to participate in the development of new therapies for HD and also improve how we think about care for HD.

More generally, Enroll-HD has normalized how we think about participating in clinical science – and that is huge.

Enroll-HD became a gateway study for the HD community, lowering the threshold for research participation. At HDSA, we have leveraged this to build a better understanding of clinical trial participation and, as a result, clinical trials are able to recruit more efficiently so that we can get scientific answers more quickly.

Can you tell us how you think Enroll-HD has improved clinical care?

Enroll-HD is very firmly part of the HD care culture in the USA. The HDSA Centers of Excellence program enables multidisciplinary care at 62 US clinics with demonstrable expertise in HD, and most of these are Enroll-HD sites. This reflects

our deliberate and specific expectation that clinical research should be integrated into clinical care, and this is what Enroll-HD is about. With most HDSA Centers of Excellence at major academic medical centers also being Enroll-HD sites, families hear about Enroll-HD all the time. This has lowered the potential barriers to taking part in research by providing a positive introductory experience that sets the stage for future clinical research participation. At HDSA, we strongly believe that Enroll-HD has helped inform the field of science to move the quality of care forward.



HD is a complicated disease and, fortunately, we have now moved past thinking of HD as ‘just’ a movement disorder. There is now an increased appreciation for the complexity of the cognitive, psychological, and mental health impacts of the disease. Enroll-HD and all that it entails have helped contribute to that awareness and understanding.

What factors do you think have been most critical to the success of Enroll-HD?

The fact that Enroll-HD is open to the entire family is a critical element in its success. It launched at a time when we were broadening our vocabulary beyond the concept of “individuals with HD” to talking much more about “HD

families”. Additionally, Enroll-HD is exciting to families because it allows folks to be part of HD science without the burden or risk of taking an investigational drug.

“Clinical research should be integrated into clinical care, and this is what Enroll-HD is about”

For families, being a part of something big like Enroll-HD is very motivating. But on a community-wide scale, perhaps even more exciting is the gravitational pull that Enroll-HD has on industry.

There are so many more companies of varying shapes and sizes now paying attention to the development of HD therapeutics. To a large extent that is because of the deliberate investment in the community and the resources that can support clinical development made possible by Enroll-HD.

The Huntington’s Disease Coalition for Patient Engagement (HD-COPE) is a global initiative organized by leading HD patient advocacy organizations that gives HD families the opportunity to voice their HD community experience to regulators, industry, and researchers working in HD therapeutic development. We asked some members of HD-COPE to let us know what Enroll-HD means to them.

Jenna Shea

Enroll-HD has allowed me, as one individual, to feel like I am making a difference in the HD community. It has been an opportunity for me to participate in a longitudinal, observational study with ease, allowing researchers to continue to learn and develop effective ways for treating HD. As part of Enroll-HD, I have come to understand and appreciate that the data collected has improved our understanding of the disease, how clinical trials are designed and conducted, how patients are cared for on a daily basis, and that my seemingly insignificant involvement played a role in discovering that information. My involvement in Enroll-HD swelled into participation in other observational studies and led to my eventual involvement in patient advocacy through HD-COPE and other organizations. It emphasized the importance of being actively involved in healthcare processes and has taught me that my day-to-day lived experience and how the disease has played out in the lives of my loved ones is valuable and can make a difference. With that learning has come an immense amount of

hope and trust in the process that, one day, an effective therapy will be available and accessible worldwide.

Tim Irwin

I’m very honored and humbled to take part in the phenomenal Enroll-HD study; not sure but this may be my 15th year of contributing to it and its predecessors. So I can’t say thank you enough to everyone at CHDI, the incredible network of HD researchers, clinicians and everyone who has had a hand in fighting so hard for Enroll-HD for continuing to build its network and grow the number of participants, and for all of the incredible learning from this important dataset. Enroll-HD has vastly improved my outlook on HD, and also improved my outlook on the prospect of effective therapeutics. Can’t wait to find out what’s next to be learned from Enroll-HD...

Robert Laycock

Being part of Enroll-HD, and PREDICT-HD before it, has been an essential part of my life for years. I would feel bereft without that connection. It’s such an easy way to feel that you are contributing in some way, not just adding data but ultimately being part of finding a cure. It makes me feel hopeful. And as a possible jumping off point for taking part in clinical trials, it points towards those effective therapeutics that are already in the works and yet to come. It’s the pool of possible participants for future clinical trials. Everyone who can should be part of Enroll-HD.

Michaela Winkelmann has been an HD advocate for many years and, since 2017, president of Deutsche Huntington-Hilfe, the main HD association in Germany. She shares her perspectives on Enroll-HD and its importance to participants and their families.



Michaela Winkelmann

What does Enroll-HD mean to the participants and families you work with?

Enroll-HD really helps people get connected with others and be part of the global perspective. Whole families, including young people, are familiar with Enroll-HD in Germany and visits are very much part of normal life. We have around 1,700 members in our association, and often when I talk to people they mention when their next Enroll-HD visit is. I regularly see people sharing their experiences of visits not just within the HD community but beyond with posts on Facebook and other forms of social media. This is something that increases awareness about what Enroll-HD is doing and people are more and more coming to understand the importance of taking part in research even if they are not ill. I think this is a really important issue for us to talk about and be open about in the HD community, particularly in terms of reducing stigma and increasing acceptance.

One thing that really stands out about Enroll-HD is that there are no age restrictions and people don't have to have symptoms. Everyone is welcome to take part and contribute to something really meaningful. For our families, it's really important to be able to do that, and I think this is why so many young people get involved. And because of Enroll-HD, people are much more aware of the other research activities they can take part in, and this

is something they are often keen to hear more about.

What else do you think Enroll-HD offers to participants?

In addition to having the opportunity to do something really meaningful, participants can sit with clinicians and talk face-to-face about their personal experiences. I think that is very helpful. The family perspective that Enroll-HD embraces means the whole family can come in for visits and this can open up important conversations, not just at the clinic but at home as well.

At Deutsche Huntington-Hilfe, we are keen to support people in supporting research! So we promote Enroll-HD in our meetings, in our newsletters, and so on. For many people, taking part in Enroll-HD is the start of taking part in other research studies and trials.

“The family perspective that Enroll-HD embraces means the whole family can come in for visits and this can open up important conversations, not just at the clinic but at home as well”

How do you think the research landscape and attitudes towards taking part in research have changed over the past ten years?

Ten years ago, only a limited number of trials were taking place, and these focused only on specific symptoms. Now, we have trials aiming to lower the huntingtin protein and effectively slow down the progression, or maybe even delay or prevent the onset of HD. I think people are really excited about that. People with children, for example, tell me they want to not only do something for themselves and their children, but the generation after that. For this to happen, it's crucial to have studies like Enroll-HD up and running. There is a lot of hope within the HD community and everybody is willing to contribute to the overall goal of finding a treatment for this family disease.



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Studies & Trials Supported

Matt Ellison is the founder of the Huntington’s Disease Youth Organization (HDYO) that offers support and education for young people affected by HD across the world. He talks about his own experiences in taking part in Enroll-HD and what Enroll-HD offers to young people.

Tell us about your own experiences as an Enroll-HD participant.

I started by taking part in REGISTRY and I’ve been going for Enroll-HD visits at my local clinic for around 10 years now, so since the beginning! It’s a really positive, enjoyable experience. As someone who is HD positive, talking with the Enroll-HD team who I know well and am very familiar with is lovely. They genuinely want to spend time with you and by providing data, information, and biosamples for future research, you feel like you personally get something out of that day’s visit.

Isolation for young people with HD can be a big problem and it is certainly something I was very aware of growing up as a young person in an HD family. For me, taking part in Enroll-HD really helps with developing a sense of community and provides the opportunity to build connections.

What else do you think Enroll-HD offers young people?

We realized through our work at HDYO that many young people aren’t even aware of the potential to take part in research. So we explain that it’s not all doom and gloom in HD, there are opportunities and genuine hope. There might not always be successes, but plenty is going on and it’s really exciting! We explain that Enroll-HD is a global study, it’s easy to do, and it doesn’t take a long time.

Talking about the value of taking part in research is a key message at HDYO, as well as for

“For me, taking part in Enroll-HD really helps with developing a sense of community and provides the opportunity to build connections”



Matt Ellison with his family

the past 10 years, and while not all of those people will be part of Enroll-HD, these efforts all help towards getting more people participating and understanding why it is important. Even if we don’t directly experience benefits from taking part, benefits are reaped by the HD community more broadly. There is not a huge amount of research that young people can participate in but Enroll-HD offers young people the opportunity to do something hugely meaningful.

One of the things we’ve been trying to tackle head on at HDYO is stigma, and while things have progressed, particularly in Western countries, it’s still a big problem and there’s a lot of work still to be done. Demystifying research is part of breaking down stigma, and we can see the various efforts

“Enroll-HD offers young people the opportunity to do something hugely meaningful”

of HDYO, Enroll-HD, and other organizations like HD-Buzz, all coming together to support that.

How do you think the HD research landscape has changed over the past 10 years and how has Enroll-HD played a role?

I think the research progress in HD over the past 10 to 15 years has been pretty amazing! And CHDI has been the catalyst for that. Obviously, Enroll-HD has been particu-



14,815⁺
Active Participants

me personally. We’ve had about 7,000 people from over 100 countries come through HDYO over

larly important in gathering such a huge amount of data – from almost 28,000 participants around the world! This makes the work of researchers and pharmaceutical companies so much easier and has enabled the progress that

we've seen so far. As much as finding the HD gene was really incredibly vital, right now CHDI is really pushing things to a whole new level with Enroll-HD and giving people hope – people who might not have had hope otherwise.

Laura Boak PhD is global development leader at pharmaceutical giant Roche for the tominersen antisense oligonucleotide (ASO) program for HD. She has worked closely with Enroll-HD throughout the development of the tominersen program.

Could you start by giving us an overview of the Roche tominersen program?

Roche partnered with Ionis Pharmaceuticals during the initial phase 1/2a trial, and the program grew from there with GENERATION HD1, the phase 3 trial of tominersen. Two different dose regimens of tominersen were compared to placebo allowing us to look at both safety and efficacy. Enroll-HD played a really big part in the planning of this trial and, at the same time, a number of other related studies that we were running.

Following a review by the independent data monitoring committee [a group of independent HD experts and statisticians who regularly review the trial data], dosing in the GENERATION HD1 trial was stopped earlier than expected [in March 2021]. The concern was that the group receiving 120mg doses of tominersen every 8 weeks appeared to be doing worse than the placebo group that didn't receive any drug. This was a devastating moment for all of us in the HD community, but the important thing is to learn from this and move forward. And so since then, we've been looking closely at the data from GENERATION HD1, GEN-EXTEND, GEN-PEAK, and the natural history study to better understand why we didn't see what we'd hoped with tominersen.



Lauren Boak with daughter, Aria, and puppy, Nala

“Enroll-HD offers an infrastructure and a platform that facilitates companies in their research and clinical trials”

So why do you think we didn't see what we'd hoped, and what are the next steps?

What we can say now, following our post hoc analyses that were not planned at the start of the study, is that younger individuals with lower disease burden tended to fare better than older individuals with more severe disease. Additionally, we hypothesize that the negative outcomes we observed were driven by tominersen exposure that was too high. So, we're now going to conduct a new phase 2 trial evaluating two lower doses to allow us to better understand if there's a window of opportunity in which tominersen has beneficial effects in this specific group of younger individuals with less advanced disease.

Importantly, tominersen is lowering both mutant 'bad' huntingtin and normal "good" huntingtin, so one of the things we need to figure out is whether the disappointing effects we saw in GENERATION HD1 were due to either the lowering of the good huntingtin or somehow related to the drug itself. These findings will be important not just for the tominersen program but for all the huntingtin-lowering approaches that are being studied at the moment, including gene therapies.

How has Enroll-HD helped the Roche program?

Enroll-HD has been phenomenally influential in all of this. HD is, of course, rare, but the field has hugely benefited from the uniquely robust, rich dataset that has arisen from Enroll-HD. When companies like Roche are new to HD, Enroll-HD provides an invaluable resource and a tremendous tool. So when we want to evaluate something like tominersen, we want to know how best to design these trials, and how to evaluate individuals with HD. One of

the key ways in which Enroll-HD has had a huge impact is in informing the selection of endpoints for clinical trials – how do you measure whether a new drug works or not? Enroll-HD, and the wider HD field generally, is unique in its openness to sharing data and ideas, and being informed about biomarkers and endpoints has been absolutely vital to our work.

Another good specific example is how we partnered with Enroll-HD to map out study sites and participants. Enroll-HD offers an infrastructure and a platform that facilitates companies in their research and clinical trials, and it continues to grow and extend its global reach.

“Of course, the participants themselves should be given credit for doing such a fantastic job!”

This is important because we want to be able to conduct HD clinical trials not just in the USA and Europe but beyond.

We also need to be able to access large numbers of potential participants, which Enroll-HD can offer. Of course, the participants themselves should be given credit for doing such a fantastic job! It’s clear that in the HD community the participants and their families have all pulled together and

that this work isn’t just about any one company and any one trial, it’s about the support network and everyone getting on board, and this is a strength that continues to grow!

Mike Panzara MD MPH is head of therapeutics discovery and development at Wave Life Sciences. He has collaborated closely with Enroll-HD during the ongoing development of their ASO program.

Tell us about the HD drug development program at Wave.

HD is caused by a mutation in the huntingtin gene that leads to the production of a toxic mutant form of the huntingtin protein. Since people with HD also still have a gene that produces healthy huntingtin protein, our focus has been to attempt to specifically reduce the toxic form of huntingtin while allowing the helpful protein to remain to do its job, which is to maintain homeostasis [balance, or equilibrium] in the body’s central nervous system.

We are targeting a specific spot on the so-called ‘mutant transcript’ that is reported to be found in just over one-third of people with HD. Our approach uses oligonucleotides [short strands of DNA or RNA] to selectively reduce the mutant protein as it’s being produced in the body.

Our first two trials failed because we just couldn’t get enough of the investigational treatment into the participants’ brain where the mutant protein is produced. So we went back to the drawing board and have now developed a new way to design our compounds to potentially increase



Mike Panzara

the amount we can get into the brain and hopefully reduce the mutant huntingtin. We’re in the midst of a Phase 1/2 clinical trial called SELECT-HD testing this hypothesis and it’s progressing really well, and we hope to have some data later this year to guide our next steps. It’s what we call an adaptive trial, meaning that we have an independent data safety monitoring committee to review the data on a regular basis and advise us on the dosing and timing of treatment to give participants. We hope this will reduce the number of people we have to recruit to answer key questions about safety and efficacy.

How has Enroll-HD played a role in this?

An essential element of these trials has been identifying individuals that we can target for treatment – just over a

third of people with HD are reported to have the single nucleotide polymorphism [SNP] that our com-

“Wave’s work with Enroll-HD has been a wonderful collaboration right from the beginning”

pound targets in their huntingtin gene, so unfortunately not everyone can take part, at least for now. When we find something that works in a subset of people then we can hopefully expand that approach to other groups of people.

Enroll-HD is one of the core sources of information we have used to identify people who may be eligible. Individuals are screened and given information so they can decide whether they would like to take part – we don't contact people directly or have access to their data.

The Enroll-HD data have been an enormously helpful tool and Wave's work with Enroll-HD has been a wonderful collaboration right from the beginning. Enroll-HD is enabling us to evaluate investigational therapies that we hope one day will translate into effective treatments for HD. This collaborative approach to research and the urgency in the search for

effective treatments as we can so readily see in the HD field is unique in clinical medicine, I think.

"I think we're at a transition point in which we're going to see many therapies emerging in the not too distant future. It's an extremely exciting time to be working in drug development in HD"

Which developments in the HD research landscape over the past 10 years stand out as being particularly important to you?

We definitely should not underestimate just how far we've come. The significant innovation and progress we've made in the development of biomarkers in HD stands out for me. The development of biomarkers in other neurological fields has greatly

accelerated treatment development. I think we're at a transition point in which we're going to see many therapies emerging in the not too distant future. It's an extremely exciting time to be working in drug development in HD.

Jim Gusella PhD is professor of neurogenetics at Massachusetts General Hospital and Harvard Medical School. He was a leading figure in the collaborative groups that mapped the huntingtin gene to chromosome 4 in 1983 and the subsequent definition of the mutation responsible for every case of HD in 1993. He is now a driving force in the Genetic Modifiers of Huntington's Disease (GeM-HD) consortium that has used many thousands of DNA samples from Enroll-HD participants and their associated clinical data to conduct genome-wide association studies and identify 'modifier genes' that can affect the age at which involuntary movements appear in people with HD.



Jim Gusella

the course of the disease. We're looking at those that impact the timing of first appearance and the rate of change in symptoms – we call these 'genetic modifiers' – and this work is critical for the development of new treatments.

How has Enroll-HD contributed to the search for genetic modifiers in HD?

When you're working in human genetics, you need two things. First, to understand what typically happens with genes in the general population, and there are worldwide efforts to define that normal genetic variation. Second, if you want to understand these processes in a specific disease, such as HD, then you need to be able to examine them in a population with that disease.

In HD, we need really large numbers of people if we are to see the effects of genetic modifiers. No single institution or research group would ever see enough individuals with HD to be able to do this.

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Nations Participating

Tell us about the GeM-HD consortium and its goals?

Our work is based on the fundamental premise that HD, while being a genetic disease that is triggered by a variation in the huntingtin gene, is also impacted by genetic variation across all the other genes in the human body, with some being more important than others. Our goal has been to define what geneticists call the 'genetic architecture' of HD and all the variation across all the genes that impact

By being able to provide data from very large numbers of individuals, characterised and defined by expert clinical investigators who understand the disease really well, Enroll-HD has brought together

what is needed to support research. Bringing together such huge amounts of data and fulfilling the requirements of what GeM-HD needs is why we have been able to identify a number of different modifier genes over the past decade. Enroll-HD has had an enormous impact. The combination of having numbers of participants and the use of standardised assessments allows for powerful statistical analyses on large groups of individuals.

“Enroll-HD has had an enormous impact... large numbers of participants and... standardised assessments allows for powerful statistical analyses on large groups of individuals”

What does the future hold for the GeM-HD consortium and Enroll-HD?

Working with Enroll-HD, our goal is now to discover and then characterize how different genetic modifiers can affect the different signs and symptoms of HD. We also want to extend our work beyond European populations [which includes North Americans of European descent], and again, Enroll-HD will provide data.

The HD community is really special with respect to participating in research and contributing towards the ultimate solution to the disease. Enroll-HD is critical for the future development of treatments in HD.

How do you think Enroll-HD has driven forward research more generally in the field?

The successes we've seen in HD over the years originally set off a torrent of studies that ultimately led to the Human Genome Project, where the idea was to map all the disease genes and the genetic variation across the genome. Research in HD is still leading the way with regard to genetic modification and genetic interaction that really come to the fore when there is something meaningful to look for, that is, something that alters the course of the disease. I think the future of common disease genetics

will be to define interactions and subgroupings as we are currently doing with HD.

“Enroll-HD is critical for the future development of treatments in HD”

The success of Enroll-HD in providing a combined resource for HD and the research successes of the last few years highlight to different disease organizations the value of the approach. It's taken success upon success to convince people - but I think that it has been worth that investment.

Darren Monckton BSc PhD is professor of human genetics at the University of Glasgow, UK, and a member of the GeM-HD consortium. His research focuses on the genetics of HD and other rare inherited diseases and has made extensive use of the Enroll-HD clinical data and biosample collection.

Tell us about your research.

We're trying to understand the genetic basis for why onset and symptoms vary between individuals with HD. We know that the primary cause of the disease is the expansion of the CAG repeat in the huntingtin gene - and that, broadly, the more CAG repeats a person inherits, the earlier their age of onset and the more severe their symptoms. But there's still a lot of variation between individuals, and two individuals inheriting the same number of repeats won't necessarily get the disease at the same time. The general idea is that understanding these



Darren Monckton and his catch of the day!

genetic differences in individuals may help reveal new avenues for therapeutic intervention.

What have been your key findings over the last 10 years?

We've known for a long time that the number of CAG repeats changes from one generation to the next and that inheriting more repeats usually results in an earlier age at onset. They can also change throughout the lifetime of the individual, frequently getting bigger, and it was commonly thought that this process may be contributing to making the disease worse over time.

Over the past 10 years, we've gone from assuming that these changes in the CAG repeat are like-

ly worsening the course of HD to being able to confirm this with direct data. This has been a tremendous step forward in understanding the disease process, and the human studies that have been facilitated by Enroll-HD have allowed us to get to this point.

Could you explain a bit more about how Enroll-HD has played a role?

Animal models have been critical to our understanding of HD biology and what might be important in humans. But to answer what is really important in humans, we need to be analyzing humans. Thanks to Enroll-HD, we have very large numbers of individuals with HD who have been well-characterized clinically and provided biological samples, including DNA. Supported by technological developments, having the huge Enroll-HD dataset is allowing us to conduct studies that wouldn't otherwise be possible.

We know that the CAG-repeat expansion causes HD, and genetic modifiers then affect how severe the disease becomes (see Jim Gusella interview). So, if some-

one inherits, say, 45 CAG repeats, in the brain that's going to slowly increase at a rate that is modified by genetic variation in so-called DNA repair genes [that have been shown to be modifier genes].

We can't easily study this directly in the brain because that can only be done at postmortem, so using data from individuals in Enroll-HD we were able to measure how

quickly the CAG repeat expands in blood cells across the lifetime. The effect in blood cells is relatively subtle compared to the way it changes in the brain. Nonetheless, we were able to show that the degree of CAG expansion was essentially proportional to an individual's age and how many repeats they started with. We believe what we are seeing in the blood is mirroring what is going on in the brain, and further data from Enroll-HD shows us that the same genetic variants in the DNA repair genes associated with more severe clinical symptoms are also associated with more expansion of the CAG repeat.

DNA repair is now firmly in the sights of drug development companies as a target

for therapeutic intervention - this is a dramatic advance from where we were 10 years ago.

What else do you think the future might hold for HD research?

I think further understanding the natural history of HD will be critical.

From a research perspective, we need

to conduct clinical trials with people who don't necessarily have the overt symptoms that we see in the later disease stages. Enroll-HD will be really important in driving this forward, given the opportunity to participate is open to everyone either with or at risk of HD.



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Published Scientific Articles

“To answer what is really important in humans, we need to be analyzing humans.”

“This is, without doubt, a team effort that includes HD families, basic scientists, and clinicians, as well as those working in pharma and biotech”

What stands out as being most important to you about Enroll-HD?

As a human geneticist, to be able to access the rich genetic data from thousands of individuals that Enroll-HD provides is amazing. It allows us to ask questions

that we simply couldn't ask otherwise. It might sound a bit geeky, but just having these sheer numbers of participants, and graphs with thousands of points on them, is unparalleled from an analytical point of view, and this is also unrivaled in other rare disorders.

Our ability to generate genetic data has rapidly increased in recent years, and the clinical data from

Enroll-HD allows us to bring this all together in a really powerful way. It's really exciting as a scientist to be able to use these data. Hopefully, this work will improve the lives of people with HD through the development of new therapeutics. It's an honor to have access to data that can make this a very real possibility.

I think the idea that thousands of HD families are willing to contribute to Enroll-HD is really inspiring to us as scientists. This is, without doubt, a team effort that includes HD families, basic scientists, and clinicians, as well as those working in pharma and biotech. What we have with Enroll-HD is an incredibly unique resource for driving forward vital research in this field.

As a clinical research platform, Enroll-HD supports additional research programs. These include nested studies such as PACE-HD, DOMINO-HD, and HDClarity that are interwoven into the Enroll-HD annual visits; this reduces the burden on participants while maintaining the high-quality data collection and logistical advantages within Enroll-HD.

Monica Busse PhD is a professor based in the Centre for Trials Research at Cardiff University, UK, and a chartered physiotherapist. She has led several multicenter observational and interventional studies related to physical activity, cognitive training, and mobility in HD, many of which have informed the evidenced-based international physiotherapy clinical guidelines.

How have you been involved with Enroll-HD?

Our PACE-HD and DOMINO-HD studies have both been nested within Enroll-HD. PACE-HD is now complete, and was our first attempt to embed a study by linking data from our exercise interventions and functional assessments with the Enroll-HD data. DOMINO-HD is still ongoing and is a purely observational study looking at a range of lifestyle factors including physical activity, sleep, and nutrition.



Monica Busse with her kids, Kate and Max

This makes it harder for researchers to run controlled studies and over the past 10 years, we've come to appreciate the importance of trying to find better ways to assess the impact of lifestyle factors on HD. In PACE-HD, we offered a sub-group of participants a bespoke physical activity coaching intervention whilst others continued with their usual activities. We wanted to learn how we could best use a platform like Enroll-HD to evaluate this kind of intervention. This worked really well with really interesting results.

How has Enroll-HD benefitted your research?

Because of Enroll-HD we have been able to recruit more quickly and effectively by having potential participant information ahead of time and accessing data that we knew had been collected according to international guidelines. Also, the sense of community that is part of Enroll-HD meant that we could advertise the study more broadly and the Enroll-HD team helped us with checking the data in a way we wouldn't have been able to do ourselves. The Enroll-HD team is fantastic to work with, and the infrastructure is already tried and tested.

The robustness around the research processes is critical to me. Take, for example, the standards required of the assessments conducted – that's really important, particularly with

 **27,899⁺**
Ever Enrolled Participants

There are really good reasons for wanting to embed lifestyle studies into the Enroll-HD

platform. People know that keeping active, eating a balanced diet, and getting enough sleep is probably good for them.

an assessment that looks at involuntary movements or is open to interpretation. Enroll-HD provides set standards and certification in how assessments are conducted to ensure data are as valid as possible.

Given the trust that HD families have placed in us in terms of their time and input, we have an obligation to give back to them. A really important part of what Enroll-HD has allowed us to do is share our data back with the scientific community.

How do you think Enroll-HD has changed the HD research landscape over the past 10 years?

I think Enroll-HD has completely transformed the way in which HD is researched. Investigators like me can come along and the Enroll-HD team listens and suggests ways in which to help. They work really hard to make research possible with the support of the Enroll-HD infrastructure. Enroll-HD has been the glue to hold us all together through its network, and also through communication and outreach.

“Enroll-HD has been the glue to hold us all together through its network, and also through communication and outreach”

“Enroll-HD has created a community of families, researchers, clinicians, and other healthcare professionals that all work together”

I don't think you could underestimate the value of Enroll-HD, and particularly the availability of natural history data, in allowing pharmaceutical companies to study disease trajectories over time. Enroll-HD is useful for individuals with HD in supporting how they take part in clinical trials, and also the pharmaceutical companies in recruiting appropriate individuals for their specific studies.

What has inspired you most about working with Enroll-HD?

For me, the most inspiring moments are when the plenary meetings come together and we see the families, scientists, and everybody together. I think for people working in other disease areas, Enroll-HD

sets a standard. Enroll-HD has created a community of families, researchers, clinicians, and other healthcare professionals that all work together. Everybody is welcomed, valued, and has a part to play. I feel incredibly fortunate to have been part of the HD world for the last 15 years!

Ed Wild MA MB BChir FRCP PhD is a professor of Neurology at University College London, a consultant neurologist at the National Hospital for Neurology and Neurosurgery in London's Queen Square, associate director of the UCL Huntington's Disease Centre, and principal investigator for HDClarity.

What is HDClarity and why is it important?

HDClarity is the first multinational, multisite collection of cerebrospinal fluid (CSF) in HD. CSF is the clear fluid that surrounds and supports the brain and spinal cord, and, consequently, it's a really valuable source of information about HD that we can't get from living people through any other means.

CSF samples allowed us to show that the drug tominersen does what we want it to do – that is, lower huntingtin – and informed the development of the first trials in which tominersen was given to people with HD. So CSF is very important for the study of biomarkers, which are things we can measure that tell us something about the human body or a



Ed Wild

disease, or how a drug is affecting the body. Biomarkers for HD can really help us to move more quickly towards effective treatments.

So how do Enroll-HD and HDClarity link together?

HDClarity is one of the largest nested studies using Enroll-HD as its foundation, it currently

has 28 active sites and we've already collected over 700 CSF samples. The core assessments for HDClarity come through Enroll-HD, and we use the same web portal to record our HDClarity data, so everything is consistent and secure.

Even though HD is a rare disease, it took us only five years to go from zero to around 700 samples, and a lot of this success

is due to the size and scope of the Enroll-HD platform. For example, a big consideration is the translation of HDClarity information and material into new languages, and the Enroll-HD platform automatically comes with a lot of that translation already built in. Enroll-HD also offers a lot more that goes on behind the scenes, such as technical and monitoring teams, and language area coordinators who help us with things like discussions with ethics boards and cultural issues at specific sites.

In the research field, HD is often seen as a pioneer when it comes to such networks and global collaborations. Certainly, Enroll-HD and all that it offers is the envy of rare disease researchers across the world due to its size, consistency, and breadth of participation.

How do you think care has been affected by Enroll-HD?

Research and clinical care are closely integrated within Enroll-HD – people might not be routinely assessed for mental health or cognitive issues in an HD clinic, but they are assessed as part of Enroll-HD. If anything on the Enroll-HD measures flags up a potential concern, this can form a useful basis for discussion between the participant and the clinical team. For people taking part without motor symptoms, issues that might not have otherwise been noticed or discussed can be brought to the attention of the clinical team, and that's an opportunity for us to give care, advice, or information to people who may ordinarily have many years in between visits or might not have sought referral to an HD clinic at all.

How do you think the HD research landscape has changed over the past 10 years or so?

One of the main changes, I think, is that we've become

much more organized, not only in the way we conduct research globally but also in our prioritization. Clearly, the biggest example of this is the advent of huntingtin-lowering therapeutics.

“Enroll-HD and all that it offers is the envy of rare disease researchers across the world due to its size, consistency, and breadth of participation”

I had the honor of giving the first dose of tominersen to a research participant in 2015, and that was the result of at least a decade of devel-

opment of that drug, from the laboratory to animal experiments, right up to the first human trial. While the phase 3 trial of tominersen, GENERATION HD1, didn't end the way we had hoped (see Lauren Boak article), this was the largest trial there has ever been in HD and the dramatic and most outstanding achievement was how quickly we were able to enroll 800 participants. Achieving that was due in large part to the organization and the infrastructure of Enroll-HD.

Drug development in rare diseases will always be challenging, but the massive Enroll-HD database that can show how many people are potentially available to be invited into trials at each site, along with their associated clinical data, really attracts pharmaceutical companies to HD. Every effort that is being made is contributing a tiny bit of ammunition to our fight against HD – and we know it's working, producing huge scientific dividends, bringing us a little bit closer to the day that we can celebrate HD becoming a treatable condition.

“Drug development in rare diseases will always be challenging, but the massive Enroll-HD database... really attracts pharmaceutical companies to HD”

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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