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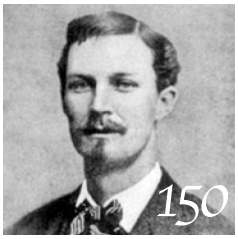
EHDN News

EUROPEAN HUNTINGTON'S DISEASE NETWORK

Scientific Advances, Achievements and Anniversaries

Catherine Deeprose



This 46th issue of EHDN *News* opens with a reflection on the 150th anniversary of **George Huntington's original description of HD**. We then turn to **CHDI's recent Annual Therapeutics Conference**, current **research efforts in Ireland**, and the development of new measures to assess function and cognition in HD. We also celebrate **10 years of Enroll-HD** and its achievements to date, and find out more about the Enroll-HD Platform Monitoring Oversight Team. Finally, we meet with the founder of the Huntington's Disease Youth Organization, **Matthew Ellison**, MBE, to hear about their 10th anniversary and ongoing, vital work with young people. With the EHDN 2022 Plenary Meeting on the near horizon, it is clear that there is much to be excited about in HD research going forward.

OUR PHOTO EXPERIMENT CONTINUES – SHARE YOUR OWN! SEE PAGE 7

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150 Year Anniversary of the Original Description of Huntington's Disease 'On Chorea' by George Huntington: A Historic Milestone Put into Context

Patrick Weydt, MD, Head of the Huntington Disease Clinic at the University Hospital Bonn and Deputy Chair of EHDN (Insta and Twitter: @huntington_doc) and Catherine Deeprose. Artwork: Gabriele Stautner

This year marks the 150th anniversary of the publication of the essay 'On Chorea' by George Huntington. He read it before the Meigs and Mason Academy of Medicine at Middleport, Ohio (USA) on 15 February 1872, and it was published in 'The Medical Examiner', a very respectable journal in its time, on 13 April of the same year. In the last few paragraphs of his understated essay, George Huntington described the salient features of the 'medical curiosity' that today carries his name. Although he believed his observations did not carry 'any great practical importance', the accuracy of his description has stood the test of time. Drawing on the records and the experience of his physician father and grandfather (with a combined 75 years of practice overseeing several generations of the families in their care, starting in 1797 in the town of East Hampton, NY), George Huntington correctly recognised the 1) 'hereditary nature', 2) 'tendency to insanity', and 3) typical adult onset of between 'the age of thirty or forty years' as characteristic features of this condition. He also pointed out that 'no treatment seems to be of any avail'.

While, in hindsight, this was certainly not the first description of what we today classify as HD, the timing and the quality of the essay allowed it to quickly spread around the world at a time when many medical eponyms were coined, assuring the family physician a place in the history of medicine.

The original text of George Huntington's essay is freely available online at https://en.wikisource.org/wiki/On_Chorea and is very much worth rereading today.

This anniversary is a welcome opportunity to reflect on the amazing progress that has been achieved in the past 150 years and the many turns and events that have shaped – and are still shaping – the history of HD and the path towards a cure. We present some of these key milestones visually in our timeline. The first events give credit to some of the predecessors of George Huntington, who independently of one another described instances of hereditary chorea that would today be classified as HD, but whose contributions, for various reasons, were not widely appreciated until long after George Huntington's essay. Then, in 1888 the German physician Johann Hoffmann filled an important gap in the description of HD by recognising some characteristics of the juvenile form of the disease as clearly distinct from the adult form (which, ironically, is often known as Westphal variant of HD, after the German neurologist and psychiatrist Carl F. O. Westphal, who described a case as far back as in 1883 but erroneously denied a connection with HD). In 1908, Gerbrandus Jelgersma, and then in 1911, Alois Alzheimer, linked HD to a degeneration of the basal ganglia, filling another void George Huntington had left open, acknowledging at the time, 'I know nothing of its pathology'.

In 1909, the eminent British geneticist William Bateson established HD as an autosomal-dominant disorder, formalising the pattern of inheritance that George Huntington had already indicated in his essay. The coincident emergence of the eugenics movement spearheaded by the infamous but influential American biologist Charles Davenport. His call for the compulsory sterilisation of HD families in 1916 portended an era of widespread stigmatisation and discrimination against the HD community that culminated in the atrocious euthanasia programs of Nazi Germany but lasted until well into the 60s and 70s of the last century. In 1955, almost unnoticed by the international world, Amerigo Negrette

reclassified the 'dancing mania' prevalent in the Maracaibo Region of Venezuela as HD, providing access to an expansive pedigree of HD families that would allow for powerful linkage analysis many years later.

The 1960s saw the emergence of organisations which to this day remain critical in the HD community. These include what is now known as the Huntington's Society of America and the Hereditary Disease Association, driven by the inspirational work of Marjorie Guthrie, wife of Woody Guthrie, and Milton, Alice and Nancy Wexler, respectively – families afflicted themselves with HD. Not long after this, the 100th anniversary of George Huntington's publication was marked by The Centennial Symposium on Huntington´s Disease in Columbus, Ohio (USA), organised by the World Federation of Neurology Research Group on Huntington's Chorea, where the Maracaibo families came to the attention of the budding HD research community. The combination of large HD kindreds with rapidly emerging tools of molecular biology revolutionised our understanding of HD, from the mapping of the HD mutation in 1983 in landmark work by James Gusella and colleagues to the identification of the specific DNA sequence ten years later by the HD Collaborative Research Group and the development of the first transgenic mouse models of the disease by Gillian Bates and colleagues in 1996. The Huntington Study Group took its roots in 1993, with a meeting organised by Ira Shoulson and Jack Penney, thus becoming the first-ever therapeutic research organisation completely dedicated to HD.

The establishment of the privately funded High Q Foundation in 2002 – the predecessor of today's CHDI Foundation – further boosted the HD research efforts, enabling the establishment of the EHDN by G. Bernhard Landwehrmeyer and colleagues in 2004. One particularly productive outcome of the work funded by CHDI is the Enroll-HD study, currently celebrating 10 fruitful years as the largest observational study of HD (and of any genetic disease to date).

In 2015, the once-distant hope of developing effective treatments for HD became a feasible reality with the publication of a genome-wide association analysis showing that the course of HD can indeed be altered by the Genetic Modifiers of Huntington's Disease Consortium. From this, progress rapidly ensued, with Sarah Tabrizi and colleagues providing the first evidence that mutant Huntingtin levels can be successfully lowered in HD patients in 2019. Also in this year, the EHDN published the International Guidelines for the Treatment of HD developed by an international task force, representing the significant strides already made in the treatment, management and care of HD.

Thus, as we reflect on the rich clinical, scientific and sociological milestones that mark the 150 years that have passed since George Huntington's seminal essay, we appreciate the importance of cooperation across disciplines and cultures for progress and innovation in the quest for a cure for HD. We approach our 2022 EHDN Plenary Meeting with a sense of just how much has been achieved so far and also filled with optimism for the future.

150 Years of Huntington's Disease Research: Some Key Landmarks

1832: First definite mention of hereditary adult-onset chorea by the English physician John Elliotson.
1842: Charles Oscar Waters provided the first written mention of HD in a letter published in Practice of Medicine.
1848: Charles Gorman published on cases of 'the magrums' (HD) in the Philadelphia area (USA) in a later edition of Practice of Medicine.
1860: Johan Christian Lund provided a description of HD on the basis of his observations in Setesdalen (Norway).
1872: George Huntington published 'On Chorea' in the Medical and Surgical Reporter. Building on earlier work by his father and grandfather, this provided the first comprehensive account of HD, which he described as 'a medical curiosity'.

1888: Johann Hoffman provided the first report on the juvenile form of HD using data from a three-generation family, noting that some characteristics differ significantly from the adult form.
1909: William Bateson, an eminent British geneticist, classified the HD pattern of inheritance as autosomal-dominant.
1908 and **1911:** Gerbrandus Jelgersma and Alois Alzheimer, respectively, correlated HD with degeneration of the basal ganglia
1916: George Davenport, an influential American biologist, called for the compulsory sterilisation of HD families.
1955: Américo Negrette presented his work reclassifying 'dancing mania' in Maracaibo, Venezuela, as HD at the Venezuelan Sixth Congress of Medical Science.
1967: Famous folk singer Woody Guthrie's affliction with HD led his wife Marjorie Guthrie to form the Committee to Combat Huntington's Disease (now the Huntington's Disease Society of America).
1968: Milton Wexler and his daughters Alice and Nancy formed the Hereditary Disease Foundation, inspired by their wife and mother Leonore's affliction with HD.
1972: The Centennial Symposium on Huntington´s Disease was held in Columbus, Ohio (USA), on the 100th anniversary of George Huntington's publication.
1983: James Gusella and a collaborative group of researchers mapped Huntingtin (HTT) to a specific gene on chromosome 4p. This was the first time a disease-associated gene had been mapped to a human chromosome.
1993: The HD Collaborative Research Group identified the DNA sequence and the precise nature of the HD-associated mutation in the HTT gene on chromosome 4, showing that the number of repeats of a specific coding sequence (CAG; cytosine-adenine-guanine) determines whether an individual will have HD.
1993: Ira Shoulson and Jack Penney launched the first meeting of what later became the Huntington Study Group (HSG) in the USA.
1996: Gillian Bates and colleagues created the first mouse model of HD.
2002: The High Q Foundation, the predecessor of today's CHDI Foundation was established as a privately funded biomedical research organisation dedicated to fast-tracking the development of treatments for HD.
2004: G. Bernhard Landwehrmeyer and colleagues set up the EHDN as a non-profit research network to advance research and clinical trials into HD across Europe.
2011: EHDN published data on the first 1,766 participants in REGISTRY. Sponsored by the CHDI Foundation, this was the first multi-lingual, multi-national prospective observational study of HD in Europe.
2012: Enroll-HD, the largest worldwide observational study of HD and integrated clinical research platform was set up to unifying REGISTRY with the North American and Australian COHORT study. This now operates across 21 countries spanning four continents.
2015: The Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium published findings from a genome-wide association analysis showing that the course of HD can be altered, opening up the potential for the development of new therapeutic targets.
2019: The EHDN published International Guidelines for the treatment of HD developed by an international task force to standardise pharmacological, surgical and non-pharmacological treatment regimens and improve care and quality of life of patients.
2019: Sarah Tabrizi and colleagues published the results of the IONIS-HTTRX trial demonstrating the successful lowering of mutant Huntingtin levels in the cerebral spinal fluid of HD patients.

'We approach our 2022 EHDN Plenary Meeting with a sense of just how much has been achieved so far and also filled with optimism for the future.'

Patrick Weydt

CHDI'S Annual Therapeutics Conference, Palm Springs, 2022

Catherine Deeprose, Simon Noble, Director of Communications, CHDI Foundation

After the hiatus on in-person meetings due to COVID-19 and an online virtual conference in 2021, researchers and clinicians could finally gather together for CHDI's 17th Annual HD Therapeutics Conference in Palm Springs which took place between 28 February and 3 March 2022. We spoke with CHDI's Chief Scientific Officer, Robert Pacifici, to find out how the long-awaited return to in-person meetings went from his perspective.

***Robert Pacifici**, PhD, is Chief Scientific Officer at CHDI Foundation. After receiving a BS from the University of Massachusetts and a PhD from the University of Southern California, both in biochemistry, his drug development career has included spells at Eli Lilly, Xencor and Amgen. Robert Pacifici now conducts his vital work in HD drug development while also a member of the board of directors for the University of California, Los Angeles Technology Development Group and an adjunct lecturer at the University of Southern California.*

It was great to see that the Annual HD Therapeutics Conference was able to go ahead in person this year. How did that feel for you personally?

We feel incredibly fortunate that we were able to hold the meeting and get everybody home safe. During the planning, we had to make the very difficult call about whether it would be safe to hold this event in person and I give a lot of credit to Robi Blumenstein, the President of CHDI, for taking it forward. The meeting organisers, Jerry Turner and Kristen Jenkins, did a phenomenal job of modifying the set-up to ensure safety for everyone involved.

I'm happy to say that it all went off without a hitch this year. Everybody made it to the conference and back home safe and sound, and for me, this is incontrovertible evidence that the HD community has a special bond. We are holding the next meeting somewhere in Europe – we typically hold the conference in Palm Springs and then every fourth year take it on the road so that it's a bit easier for our European colleagues to be able to attend without a transatlantic flight. That's something that we're looking forward to, probably in April 2023.

2021 was a difficult year in many ways. In addition to the challenges of COVID-19, we saw significant setbacks in terms of clinical trials and drug development. What are your thoughts on the current state of play in HD research?

There's no doubt that, on many levels, the HD community took a couple of punches to the gut with these recent setbacks. I can only imagine how that feels for HD patients and their families, and it must have just been devastating to hear that news.

To my mind, the Roche and Wave Life Sciences trials still represent the first very credible, custom-crafted therapeutic candidates for HD. The whole HD field has worked collaboratively to enable these efforts in a variety of different ways. But I think we have to be level-headed about the typical odds of success in drug discovery in general and in neurodegeneration in particular. It really would have been a dream come true for the first shot on goal to pan out the first time. The interventions themselves and the therapeutic modalities identified thus far are going to allow us to learn about the selection of research participants. We will also learn about the design of clinical trials such that we can either walk away from a particular modality/mechanism of action or figure out how we would do it again in a

different, better way.
Roche has been very open and gracious about the sharing of data and findings with researchers, clinicians and families in a way that allows the whole HD community to figure out what we can extract from these experiences. Taking a rational perspective, perhaps the most important thing is that these experiences have not 'poisoned' the approach; nobody took from these clinical trials that somehow lowering huntingtin is no longer a viable therapeutic strategy.

> *'I'm more confident than ever that we're on the right track towards therapeutic interventions that will make very meaningful improvements in the lives of those affected by HD.'*
>
> **Robert Pacifici**

This is really important because many efforts are ongoing, including the trials by Novartis, PTC Therapeutics and UniQure, and several others are also in late-stage preclinical or early-stage clinical development. Clearly, if any of these companies believed that huntingtin lowering was no longer viable they would pull their programmes – but they haven't. I've got my fingers crossed that, almost three decades after the discovery of the causal gene, we're finally going to understand what we need to do to lower huntingtin, how much we need to lower it, and what forms of huntingtin we need to lower.

One of the things that have really impacted my thinking is the degree of granularity and sophistication that is required to tackle HD. It's not just a bad gene and it's not just a bad protein. But, given the pace of research progress and the current state of the drug development pipeline, I'm more confident than ever that we're on the right track towards therapeutic interventions that will make very meaningful improvements in the lives of those affected by HD.

• • •

European Huntington Association

Astri Arnesen, President

The European Huntington Association (EHA) has invited Spain to be part of the Moving Forward project. Following on from this, the first national and first-ever national meeting for pre-symptomatic, at-risk and gene-negative people took place in Spain (see https://ehamovingforward.org/2022/05/first-moving-forward-national-meeting-in-spainthe-uncertainty-of-waiting-may-7th-2022/), and Ruth Blanco, the president of ACHE (Asociación Corea de Huntington Española), has integrated the team as Moving Forward National Coordinator.

At the end of 2021, a country-specific survey about the perceptions and experiences regarding research participation was conducted among the persons at-risk and persons with pre-manifest HD. The survey results have allowed the team to identify the real needs of the Spanish HD community, and enabled the design and implementation of appropriate actions to address these issues. There are many more actions in the Moving Forward Spain project pipeline and the team is extremely motivated to address the needs, worries and wishes of a welcoming HD community.

At EHA, we have also started a new moderated forum to allow people to exchange thoughts, experiences and opinions about different aspects of dealing with HD. While the forum is very new, the number of visits are indicating great interest from HD families, and health care professionals can also learn more about first-hand opinions and experiences of HD: https://ehamovingforward.org/community/

Send Us Your Photos!

This edition's photo features EHDN's Georg Bernhard Landwehrmeyer, Patrick Weydt and Jenny Townhill. Patrick explains, *'After a wonderful meeting at the CHDI's Annual Therapeutics Conference in the gorgeous setting of a Palm Springs resort, we found ourselves seated together by chance on our return flight in the reality of Economy Class!'*. You can read more about the conference in our interview with Robert Pacifici here.

Our photo experiment continues!

Whether you're affected by HD personally, or you're a carer, clinician or scientist working in the field, we'd like to publish your images in the newsletter. If you have a photo that provides an insight into your daily life, that you think might interest or inspire other EHDN members – or make them think differently about the disease – please send it to us along with a few words explaining who you are and what the image shows: **newsletter@euro-hd.net**

Insight into the Enroll-HD Platform Monitoring Oversight Team

Jenny Callaghan, Training and Compliance Manager

In addition to being an important study in its own right, Enroll-HD's function as a platform to support additional studies and research projects is a vital tool in the HD research effort. The Enroll-HD platform provides data and samples to HD researchers to assist their studies and research projects, as well as infrastructure, resources and support. This allows studies to get off the ground and make the most of the experience and expertise built up over 10 years of Enroll-HD.

From left to right: Ruth Fullam, Jenny Callaghan, Selene Capodarca

One of the key areas the Enroll-HD platform can provide support to other studies is in the monitoring of data. The Enroll-HD monitoring team ensures researchers and those running additional studies and research projects using the Enroll-HD platform receive the highest quality data from Enroll-HD. The team can also monitor platform studies alongside Enroll-HD at regular Enroll-HD monitoring visits, reducing the burden on sites, and increasing efficiency.

As the Enroll-HD platform grows and more studies take advantage of the benefits the platform can offer, effective coordination of the monitoring effort is critical. The Platform Monitoring Oversight Team (PMOT) was set up for this very reason in 2018. Led by Enroll-HD Global Project Manager, Selene Capodarca, and myself, the team includes lead monitors from each of the Enroll-HD regions, and representatives from all of the relevant Enroll-HD platform studies as well as representatives from the Enroll-HD Periodic Dataset (PDS) and Specified Dataset preparation teams. PMOT meets every other Tuesday. The main job of the PMOT is to 'connect the dots' across the Enroll-HD platform, ensuring each study's requirements for monitoring are clearly communicated and prioritised. The team is also responsible for standardising monitoring processes across the Enroll-HD platform, ensuring that monitors can work as efficiently as possible.

> *'The main job of the PMOT is to "connect the dots" across the Enroll-HD platform, ensuring each study's requirements for monitoring are clearly communicated and prioritised.'*
>
> ***Jenny Callaghan***

PMOT is currently working on coordinating the monitoring effort for four active platform studies, two additional studies in start-up, and multiple specified dataset requests. In addition, the PMOT is also working hard on plans to reduce the Enroll-HD monitoring backlog which has accumulated over the last 2 years due to the COVID-19 pandemic, including monitoring of the plasma collection in preparation for the 2022 Periodic Dataset release (PDS6).

With the number of dataset and samples requests and platform studies expected to increase over the next 12–24 months, the PMOT is striving to streamline and improve processes to guarantee the continuing delivery of data and samples to the HD research community, ensuring the Enroll-HD platform lives up to its potential.

Developing New Measures to Assess Function and Cognition in HD: FOCUS-HD

Matthew Roche, Director of Outcomes Research at CHDI Foundation, tells us about an exciting new programme of research developing and validating new measures of cognition and function in HD.

As clinical trials are increasingly looking at earlier stages in the progression of HD, we need measures that can accurately reflect the changes that are happening. Unfortunately, current measures aren't able to do this effectively. In FOCUS-HD, we are evaluating two measures that may address this unmet need: the Functional Rating Scale 2.0 (FuRST 2.0) and the Huntington's Disease Cognitive Assessment Battery (HD-CAB). Both have been in development for more than 10 years. The FuRST 2.0 aims to assess people with HD's functional abilities and the HD-CAB was specifically developed to test people with HD's cognitive abilities.

> *'As clinical trials are increasingly looking at earlier stages in the progression of HD, we need measures that can accurately reflect the changes that are happening.'*
>
> ***Matthew Roche***

When it comes to the assessment of functional abilities in people with HD, the Total Functional Capacity (TFC) scale (part of the Unified Huntington's Disease Rating Scale) has been used to assess function in HD for a very long time, including as an endpoint in clinical trials. But we know that it is not very sensitive to detecting changes in functional abilities, especially when the signs and symptoms of HD are first starting to emerge. For example, people with HD and their loved ones report them as having difficulty at their jobs, often with more difficult work tasks, but these aren't detected on the TFC scale. The FuRST 2.0 is designed to pick up on these changes and thereby, allow us to understand and track the impact of HD in a manner that was not previously possible.

The HD-CAB is a battery of tests used to assess different aspects of one's cognitive skills or thinking abilities – things like attention, memory, and emotional recognition. The tests for the HD-CAB were selected based on their ability to detect differences between people with HD, at various stages of the disease's progression. What we do not yet know is whether the HD-CAB is able to track changes in cognition in people who have HD or the amount of change that is required on the HD-CAB tests to reflect a change that people with HD would consider meaningful.
In FOCUS-HD, validating the FuRST 2.0 is the main priority, and we are also trying to contextualise changes in the HD-CAB as they relate to changes in the FuRST 2.0 and other measures that reflect change that is clinically meaningful. To accomplish this, we are initiating a research program called FOCUS-HD and it will consist of three component studies:

Our first study is called FOCUS-Online. People will self-report their HD status (e.g., diagnosis, gene-expansion carrier) and complete the FuRST 2.0 and a few other questions to help us determine disease progression. This will allow us to determine if people understand the questions that we are asking of them, if there are any wording issues or problematic questions, and also if the response options are appropriate.

The second study, FOCUS-In Person will consist of participants in Enroll-HD who will be given the opportunity to complete the FuRST 2.0. We will start with the sites based in the USA because the scale itself is written in American English. Once the psychometric properties of the FuRST 2.0 are confirmed, we will then work on translations and cultural adaptations.

The third study, FOCUS-Longitudinal, is further down the pipeline. This will consist of nine study visits conducted over three years. Here, we will characterise the natural history of how functional and cognitive abilities in HD change in terms of the FuRST 2.0 and HD-CAB. With a large sample of 500 planned participants, this will be a challenging but important study. We are eager to engage and work with the HD community in the development of these important measures, as we hope they will aid in the development of treatments that provide meaningful benefit to people with HD.

Trinity College
The University of Dublin

Trinity College Dublin/ Beaumont Hospital Huntington's Disease Research Team

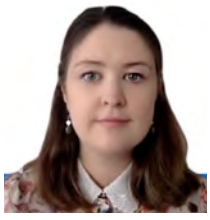
Niall Pender, Colm Peelo, Mairead Fallon, Roisin McMackin, Sarah Darcy, Orla Hardiman

Niall Pender

Orla Hardiman

Roisin McMackin

Colm Peelo



Sarah Darcy

Mairead Fallon

The HD research team in Beaumont Hospital and Trinity College Dublin has been carrying out research into HD since 2012. It is led by Niall Pender who has been the local PI for the Enroll-HD study since 2015. We collaborate closely with Orla Hardiman in the Academic Unit of Neurology, Trinity College Dublin. Our HD research team is affiliated with Academic Neurology at Trinity College Dublin, which has expertise in the psychology, epidemiology, neurology and electrophysiology of neurodegenerative diseases. We have also been very lucky to have close links with our national HD advocacy organisation the Huntington's Disease Association of Ireland, without whose support and assistance we would not have been able to progress our research programmes.

Our team is running a number of HD research streams in addition to Enroll-HD. One of our primary studies is HD-Cog, which was born out of a need to capture an in-depth picture of the evolution of cognitive and behaviour change in HD over time in the search for more sensitive cognitive biomarkers of progression and early signs of cognitive impairment in pre-manifest gene carriers. In this study, we are characterising the cognitive and behavioural profile of HD patients in Ireland, and beginning to uncover the incidence and prevalence of HD-cognitive impairment in the Irish population using longitudinal neuropsychological assessment. There have been no previous epidemiological studies of HD in Ireland.

In addition to this study, we are collaborating with Sharon Abrahams at the University of Edinburgh to standardise and validate the use of a robust cognitive screening tool for HD. The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) is a well-validated and repeatable cognitive screening tool which has been developed and standardised in patients with Motor Neurone Disease. We are currently validating its use in people with HD and we anticipate that the ECAS will permit better evaluation of cognition and behaviour in clinics and research.

In addition to the examination of patient cognitive functioning and wellbeing, our HD-Carer study assesses how HD can impact caregiver wellbeing and burden. The aim of this study is to identify the clinical needs of HD patients and their caregivers in order to advocate for better clinical services and in anticipation of further psychological intervention studies.

A new project in the group run by Roisin McMackin employs transcranial magnetic stimulation and electromyography to assess the connections between cognition-, motor planning- and motor execution-controlling cortical regions, in search of electrophysiological biomarkers of neurodegeneration. Our aim in this project is to improve the detection of cortical network dysfunction in pre-manifest patients as they approach manifest HD, and improve our understanding of the physiology underpinning the relationship between the cognitive and motor aspects of HD. Results from this study may also allow early evaluation of drug candidates in clinical trials, as electrophysiological biomarkers are used as surrogate endpoints above the sensitivity of clinical motor and psychological examination, and could also potentially offer prognostic information about onset and rate of decline in motor and cognitive system dysfunction.

Like many centres, our studies were impacted by COVID-19 and the need to restrict patient access to the hospital. However, our team has been able to create secure and valid online platforms to continue our research programmes. We hope to be able to increase HD family participants throughout our studies over the coming months. We also hope to develop further collaborations with colleagues in the EHDN and would be delighted to connect with other centres across Europe (email: pendern@tcd.ie)!

Photo: Jenny Townhill

Photo: G. Stautner, Artifox.com

Update: Clinical Trials

Jenny Townhill and Tim McLean, Central Coordination

The following studies have been endorsed by EHDN. Endorsement of a study protocol follows review by the EHDN Scientific and Bioethics Advisory Committee, which makes its recommendations to the Executive Committee. If endorsed, a formal letter of endorsement is then issued to the study sponsor, allowing them to inform relevant regulatory authorities and/or ethics committees that the study protocol has been reviewed and endorsed by a group of expert HD scientists and clinicians. The endorsement may also be posted on the EHDN website, signalling the same message to the HD community.

Key updates since the last newsletter are provided below for EHDN-endorsed trials and studies; please refer to Table 1 for a summary of the main study information.

SOM3355 (SOM Biotech)

This study, exploring the efficacy and safety of SOM3355 (bevantolol) in treating chorea, has started activating sites in Spain, with recruitment anticipated to start soon. Approximately 20 sites are expected to be activated across Europe in the next quarter.

GENERATION-HD1 and GENEXTEND (Roche)

The last participant visits have now been conducted and the studies are closed. Analysis of the full data set is ongoing with further results to be presented at conferences this year. An initial analysis of the digital biomarker data was presented at the CHDI annual therapeutics conference (see https://chdifoundation.org/2022-conference/)

HD-DBS (Heinrich-Heine University, Düsseldorf)

This multicentre trial exploring the safety and efficacy of deep brain stimulation in 48 people with HD completed recruitment in 2021 and preliminary analyses of the 3-month data have been completed. The initial results were presented at the CHDI annual therapeutics meeting (see https://chdifoundation.org/2022-conference/)

DOMINO-HD (Cardiff University)

DOMINO-HD is the first study to integrate prospective longitudinal digital physical activity and sleep tracking with nutrition assessments and novel (as well as more commonly used) clinical assessments to explore the interplay between environmental factors and HD outcomes. Recruitment closed in April 2022, with 100 participants recruited. Despite not meeting the intended study recruitment target of 300 due to various logistical and regulatory challenges including the COVID-19 pandemic, this will be the largest ever longitudinal HD lifestyle metric dataset capturing physical activity and sleep behaviour over 12 months. To aid the interpretation of this dataset, digital device validation studies have been completed in Cardiff, Burgos and Zurich. The analysis of these data is now underway. The DOMINO-HD dataset with associated Enroll-HD clinical data will, in the future, be made available to the HD research community upon specific request.

The DOMINO-HD study is funded through the EU joint program for Neurodegenerative Disease Research as part of the JPND funding call into Health and Social Care (2019), with funding from the Alzheimer's Society, Secretary of State for Health and Social Care, Health and Care Research Wales, Public Health Agency Northern Ireland, Jacques and Gloria Gossweiler Foundation, Bundesministerium für Bildung und Forschung, Narodowe Centrum Badań i Rozwoju, Swiss National Science Foundation and the Health Research Board.

HDGeneTRX2/AMT-130-2 ()

This open-label gene therapy trial of AMT-130 in people with early manifest HD is planned to be conducted in Poland, Germany and the UK. 15 participants are expected to be enrolled in total, and the first dose cohort of six participants was recruited in Poland and completed in March 2022. The data from this European study will be used in combination with the ongoing US study; in total, 59 patients are expected to be enrolled in both studies and the results will establish safety, proof of concept, and inform the optimal dose for a Phase III trial, or a confirmatory study if an accelerated registration pathway can be pursued.

PTC518 (PTC Therapeutics)

The PIVOT-HD study, a Phase II trial of PTC518 (an oral small molecule huntingtin lowering compound) planned to be conducted at sites in the US and Europe, has been initiated in the US. A previous Phase I trial of PTC518 in healthy volunteers showed a dose-dependent effect of huntingtin protein lowering. Building on these results, the PIVOT-HD trial will investigate the safety and tolerability of PTC518 and explore its effects on HD biomarkers in blood, cerebral spinal fluid and imaging.

Table 1: EHDN-endorsed Trials and Studies

(Active or in Start-up)

Registration ID (ClinicalTrials.gov)	Sponsor	Trial name	Phase	Intervention	Mechanism of Action	Target Enrolment	Location(s)	Status
N/A	Cardiff University	DOMINO-HD	N/A	N/A	N/A	300	Poland, Spain, Switzerland, UK	Participant follow-up
NCT02535884	Heinrich-Heine University, Duesseldorf	HD-DBS	II	Deep brain stimulation	High-frequency stimulation of the Globus Pallidus	50	Austria, Germany, Switzerland	Complete
NCT05111249	Novartis	VIBRANT-HD	IIb	branaplam	Small molecule mRNA splicing modifier	75	USA, Canada, Europe	Recruiting
NCT04556656	Prilenia Therapeutics	PROOF-HD	III	Pridopidine	Sigma-1 receptor agonist	480	USA, Canada, Europe	Participant follow-up
NCT05358717	PTC Therapeutics	PIVOT-HD	II	PTC518	Small molecule mRNA splicing modifier	TBD	Australia, France, Germany, Netherlands, UK, USA	Recruiting
NCT03842969	Roche	GEN-EXTEND	OLE	Tominersen	Allele-nonselective ASO	1,100	Canada, Europe, USA	Complete
NCT03761849	Roche	GENERATION-HD1	III	Tominersen	Allele-nonselective ASO	801	Australasia, Canada, Europe, Japan, USA, Latin America	Complete
EudraCT: 2021-003453-28	SOM Biotech	SOM3355	IIb	SOM3355/ bevantolol	VMAT2 inhibition	129	France, Germany, Italy, Poland, Spain, Switzerland, UK	In start-up
NCT04406636	Triplet Therapeutics	SHIELD-HD	N/A	N/A	N/A	60	USA, Canada, Europe	Participant follow-up
NCT04120493	UniQure	HD GeneTRX2/ AMT-130-02	Ib/II	rAAV5-miHTT	miRNA nonselective (gene therapy)	26	Germany, Poland, UK	Recruiting
NCT05032196	Wave Life Sciences	SELECT-HD	Ib/IIa	WVE-003	Allele-selective ASO	36	Australia, Canada, Europe	Recruiting

ASO = antisense oligonucleotide; OLE = open label extension

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Photo: G. Stautner, Artifox.com

Update: Enroll-HD – Status and Recent Milestones

Olivia Handley, Enroll-HD Global Platform Manager

Participant #1: 27 July 2022 marks the 10th anniversary of the first participant to be recruited into Enroll-HD by a relatively small study site (University of Tennessee, Memphis, USA). At the time, Operations Director for Enroll-HD, Joe Giuliano wrote *'today in Memphis, Tennessee the first patient is being seen as we speak. It really has been a team effort, and everyone has been and is going all out to get this done…'*. That sentiment is still very much front and centre as to how Enroll-HD happens – the continued commitment, hard work and enthusiasm brought by the Enroll-HD team, participating sites and most of all the HD community enables Enroll-HD to be a successful research platform.

1,000 participants recruited at a single site: Earlier this year, we celebrated two Enroll-HD sites reaching the incredible milestone of 1,000 participants ever enrolled. Congratulations to St. Josef and St. Elisabeth Hospital GmbH, Bochum (Germany) and Lega Italiana Ricerca Huntington, Rome (Italy). In addition, George Huntington Institute GmbH, Münster (Germany) is on course to recruit their 1,000th participant in July.

Enroll-HD has more than **27,000 participants** ever enrolled, and over 21,000 participants are still enrolled. Enroll-HD study metrics have been closely monitored throughout the pandemic period. One dramatic (and perhaps unsurprising) change that we have observed during this period is the steady decline in the number of active study participants. This is the first time that a downward trend has been observed for this metric since the study began. While the number of participants entering the study continues to exceed the number of participants definitively exiting the study, the active sample continues to shrink. This may be driven by participant reluctance or inability to attend study visits due to pandemic-related health concerns or site closures/restrictions. We hope that this is a temporary trend, as maintenance of a large, active sample is crucial in supporting Enroll-HD's goal to support clinical trials and studies. We are aware of the challenges and restrictions dictated by the pandemic, and we would like to express our appreciation for encouraging the participants to return to the site for their annual visit.

156 sites from 23 countries are active in Enroll-HD including the first site in Peru which was activated in June 2022. A further 17 more sites are in start-up. We continue to manage Enroll-HD across North America, Latin America, Europe and Australasia and are strongly encouraged by the platform's ability to grow and bring together the HD research community across borders.

801,176 biosample vials have been collected since Enroll-HD started. The Enroll-HD biosamples collection is unparalleled and has supported over 33 biosamples distributions. Our understanding of the biological pathways in HD has been significantly advanced by the samples collected through Enroll-HD. For example, Enroll-HD's very large DNA collection (23,459 unique DNA samples from whole blood) allowed genome-wide association studies to inform about possible genetic modifiers and further supported drug development programs focusing on genetic features.

98 peer-reviewed publications using Enroll-HD data have been generated. Every two years, Enroll-HD produces a high-quality PDS. To date, the PDS has been downloaded over 230 times. A further 112 specified dataset requests (that include certain data

not typically available in the PDS; require review/approval by the Enroll-HD Scientific Review Committee) have been made available for download. The quality and volume of data made available to the research community are two of the greatest achievements of the Enroll-HD platform. Please visit www.enroll-hd.org/for-researchers for more information on accessing Enroll-HD data and biosamples.

21 studies and **23 clinical trials** have been supported by the Enroll-HD platform. Each year, more studies and trials approach the platform for support and resource, whether this is for recruitment, training, linking to Enroll-HD data, monitoring, or site selection. This activity demonstrates Enroll-HD's versatility as a research platform that can be used to support many studies and trials.

'The major aim of Enroll-HD is to accelerate HD therapeutic development. These milestones and achievements each speak to the platform's successes in meeting that aim. We very much look forward with anticipation to seeing what the next 10 years of Enroll-HD will bring to the HD community.'

Olivia Handley

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Now available:

The MDS-ES and EHDN Joint Online Course Series:

Huntington's Disease: From Foundational Principles to Assessment & Treatment

An opportunity for neurologists, neuropsychiatrists, movement disorders specialists and other healthcare professionals who are improving their knowledge of HD to receive in-depth information from internationally recognised HD experts.

Log in here to enroll:
https://education.movementdisorders.org/Detail/577/MDS

Get in touch with the Think Tank!

The EHDN's HD Science Think Tank brings together EHDN members and staff who are closely involved in supporting scientific research – including members of the Executive Committee, Central Coordination and the working groups – and it engages with the HD research community in three ways:

- Researchers may contact the Think Tank for help in identifying potential collaborators or funding opportunities, or to discuss scientific ideas
- The Think Tank welcomes suggestions of research topics, and has provided a contact form on its website via which these can be submitted
- The Think Tank may occasionally propose specific research topics that could be addressed by a dedicated task force working for a defined period of time

For more information about the Think Tank, please contact Kristina Bečanović:
kristina.becanovic@euro-hd.net

Photo provided by Kristina Bečanović

Update: HDClarity

Seema Maru, HDClarity Study Coordinator and Alex Lowe, HDClarity Research Assistant

Current Site Status

With the growing numbers of clinical trials exploring novel therapeutic approaches for treating HD, HDClarity was designed to:

GENERATE: Generate a collection of high-quality cerebrospinal fluid (CSF) and plasma (from blood) samples from six patient cohorts: Healthy Controls, Early Pre-manifest HD, Late Pre-manifest HD, Early Manifest HD, Moderate Manifest HD and Advanced Manifest HD.

COLLECT: Collect clinical data to assess characteristics of HD by conducting cognitive, movement and neurological tests, CSF and blood and collection of medical history.

RESEARCH: Samples can be requested by investigators for further research and analysis to help understand HD processes, identify new biomarkers and develop novel treatments for HD and other neurological conditions.

All HDClarity participants must be on the ENROLL-HD study and since 2016, HDClarity has opened across seven nations worldwide and has over 500 participants. Our current active sites are located across the UK, Canada, USA, Germany, Italy, Poland and Spain. We are hoping to open more sites in Austria, Australia, France, Netherlands, Norway, New Zealand, Portugal and Switzerland. Recently, the study was opened in new sites within Great Britain and Germany despite the COVID-19 pandemic and lockdowns. Across all of the currently active sites, Germany continues to be the highest recruiting country for HDClarity (see Figure 1 below).

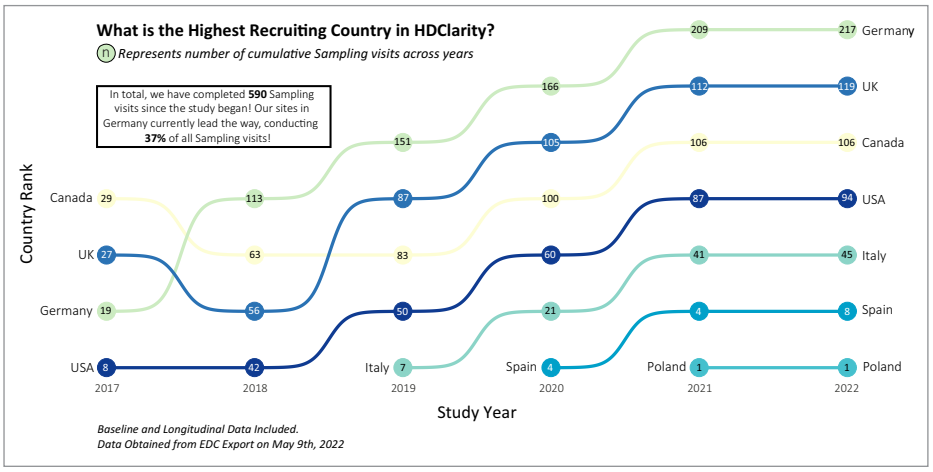

Figure 1: Recruitment by Country and Study Year

Total Recruitment

As of May 2022, our total recruitment stands at 656 participants and 685 samples across all participant groups (see Figure 2 below).

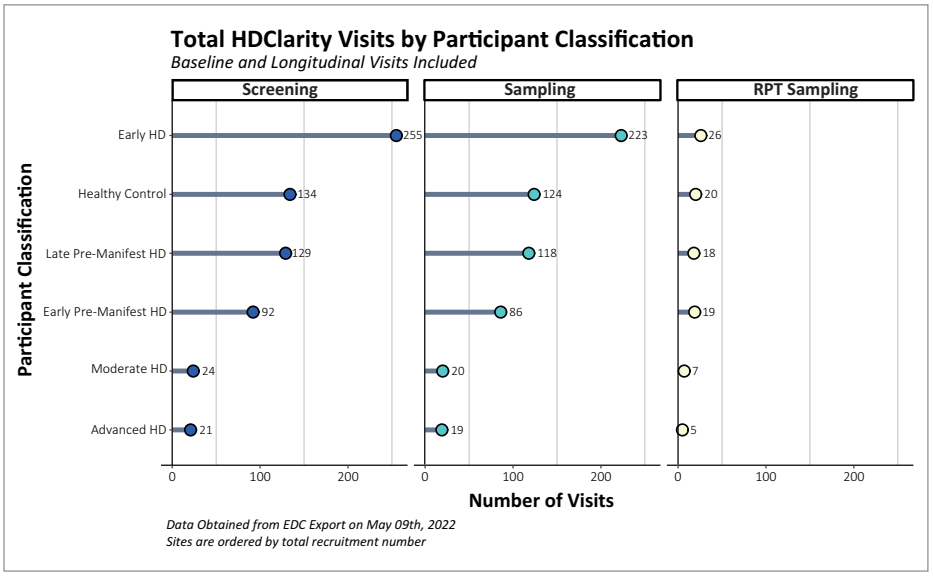

Figure 2: Total number of Initial, Sampling and Repeat (RPT) Sampling Visits Conducted Across Participants in All Diagnostic Categories (up to 01 April 2022)

Longitudinal Visits

Initially, after one screening and sampling visit (with an optional repeat visit if applicable), a participant's role in the study was considered complete. However, the implementation of Protocol Version 3 provided

participants with the option to consent to repeat the screening and sampling visit on an annual basis. This is termed a longitudinal visit and participants are free to choose whether they would like to attend these visits. The introduction of **Protocol Version 4.1** will result in participants consenting to four Annual Screening and Sampling Visits (i.e., at 1, 2, 3 years after the first initial visit), with re-consent thereafter.

We are pleased to announce that in February 2022, Royal Devon and Exeter Hospital (UK) became the first site to recruit a participant under the new version of Protocol V4.1 with University College London Hospital (UK) recruiting their first participant in March 2022. We are currently aiming to transition all active sites to Protocol V4.1.

Further Information

The protocol and further information are available at www.hdclarity.net and the study team, led by Professor Ed Wild is always happy to answer any questions.

Finally, we would like to thank all the study volunteers and clinical research facilities who have given their time, dedication, and commitment to HDClarity. Your continued support has been invaluable and directly contributes to the success of the study.

For more information and details on participating in HDClarity, please email hdclarity-cc@enroll-hd.org

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Huntington's Disease Youth Organization (HYDO)

Jenna Heilman, HDYO Executive Director

Jenna Heilman

JOIN-HD Registry

HDYO's Juvenile Onset HD Global Registry (JOIN-HD) has pre-enrolled 50 patients and family members from 10 different countries. This is an exciting milestone as the registry just launched this past February. The aim of this registry is to locate and connect people impacted by JoHD, understand unmet needs and hopefully influence future research. We are also honoured to have an incredibly committed Scientific Oversight Committee to support JOIN-HD, including Martha Nance, Jean-Marc Burgunder, Leon Dure, Helen Santini, Oliver Quarrell, Benjamin Wilfond, Peg Nopoulos and Ferdinando Squitieri.

To learn more about JOIN-HD, email registry@hdyo.org.

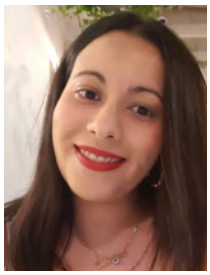
HDYou: Community Stories

This is a series of interviews by the HD Community for the HD Community. Topics will include perspectives which empower, personal stories, ways to get involved and scientific updates. Our first segment included a unique perspective from Michael Hayden from Prilenia Therapeutics on YouTube about his background and providing hope to young people.

Update: New Seed Funds Awarded

Catherine Deeprose

The EHDN has recently awarded seed funding for two exciting new projects.



Christiana Christodoulou

Christiana Christodoulou at the Cyprus Institute of Neurology and Genetics has been awarded funding for her project aiming to complete untargeted proteomics analysis and proteomic profiling in Cypriot HD patients. More specifically, this work will examine how proteins interact with other proteins and how abnormal protein expression changes in different HD disease stages (Project PI: Eleni Zamba Papanicolaou).

Patrick van der Wel

Patrick van der Wel at the University of Groningen (Netherlands) has been awarded funding for his project exploring how conformation-specific antibodies target misfolded huntingtin states. This research will develop a molecular understanding of particular huntingtin-specific antibodies to support their use as diagnostic tools in preclinical research and beyond.

Seed funds are intended to support pilot studies that will eventually kickstart larger projects. The next deadline for applications are 1 November 2022 and 1 March 2023. More information about the programme and how to apply can be found here or you can contact Christine Capper-Loup (Christine.Capper-Loup@siloah.ch) for further information.

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Update: Funding Opportunities

Fionnuala Margreiter, Grants & Collaborations Manager

Two Marie Skłodowska-Curie Actions calls are now open:

- **Postdoctoral Fellowships**
- **Doctoral Networks**

For more information visit https://europa.eu/!ckwRr4

MSCA4Ukraine: A new scheme to support displaced scientists from Ukraine

#MSCA4Ukraine will provide fellowships for doctoral candidates and postdoctoral researchers to continue their work in EU Member States and countries associated with #HorizonEU.
For more information visit https://europa.eu/!KVrMnb

Two other calls will open in autumn:

- **Staff Exchanges** (Call opening 6 October 2022, Deadline 8 March 2023)
- **COFUND** (Call opening 11 October 2022, Deadline 9 February 2023)

Marie Skłodowska-Curie Actions: Current and Upcoming Calls

The Marie Skłodowska-Curie Actions (MSCA; European Union's reference programme for doctoral education and postdoctoral training) provide grants for all stages of researchers; careers and encourages transnational, intersectoral and interdisciplinary mobility.

For other grant opportunities, please visit the EHDN Grants & Collaborations page (http://www.ehdn.org/hd-clinicians-researchers/grant-manager/) and follow me on Twitter @EHDN_GRANTM

Interview with Matthew Ellison, MBE: Founder of the Huntington's Disease Youth Organization

Matt Ellison, the founder of HDYO, was awarded an MBE in 2021 in recognition of his work supporting young people across the globe with HD. Here, we catch up with Matt to hear about his award and plans for the future.

Wow! A Member of the Order of the British Empire – congratulations! How did you react when you heard the news?

I actually hung up on the phone call because I thought it was a joke! Not just once but three times. I was like 'yeah mate, good one but I don't think so.'

'We're definitely in a better place than we were 10 years ago but there is still lots of work to do.'

But it wasn't a joke! Have you received your award now?

No, I haven't. Because of COVID, there's a huge backlog, and for various reasons, I've postponed a couple of times but I think it's going to be a great experience.

It seems that HD is increasingly gaining awareness in lots of different ways, would you agree?

Absolutely, yes. This awareness is growing due to the media and TV shows and in general, there's a lot more going on and deservedly getting attention. Charles Sabine, for example, recently received an award for this work in raising awareness of HD. It can be hard to get noticed and I think this all helps keep people motivated. You know, people kindly volunteering for trials and researchers working in search of treatments. I think it's good to keep that momentum going on in this way.

So, 2022 is HDYO's 10th anniversary! What sort of things have you been doing to mark this important date?

We did the virtual Congress in March this year and we're also doing a lot on social media. It's pretty fantastic for us that we've turned 10 years and still doing good work. I'm very happy with what HDYO has achieved so far and the progress made through our own work and also that of the HD associations across the world. Previously, youth services weren't available and young people were isolated. We're definitely in a better place than we were 10 years ago but there is still lots of work to do.

COVID has of course been a challenge but hopefully, we're moving out of that now and going in a more positive direction.

Thinking about the successes of the past 10 years, is there any part that particularly stands out for you in terms of HDYO and the work you've been doing?

We have over 7,000 contacts now around the world, from across more than 100 countries. Being global and being accessible are both really important to me. One of the ways we've achieved this is by making the website available in as many languages as possible. This means that young people can go online, and learn about HD in Spanish, for example, but also, ask questions and get support in Spanish. I think it's very, very important that young people feel they can reach out like that in their own language. That's something I'm very proud of. Also, the camps we've held and the events we've done around the world have been really impressive (although I'm biased!). We've done about 10 camps around the world (across North America, Australia, New Zealand and Europe) and they were really fantastic experiences for the young people. I loved attending these and seeing the young people connect, support one another and interact with the volunteer staff.

Because of the international focus of your work and also the focus on young people, it seems that when the pandemic struck, you

were already a step ahead in terms of having so much available online…

Yes – but we really missed the in-person events. We've done two virtual congresses now and they've both been big successes but they're still virtual and for me, it's not quite the same. We've all missed the meeting in person and that was a big part of what HDYO was doing. Those events would allow you to have face-to-face contact and spend time with people, allowing them to reach out.

'We've all missed the meeting in person and that was a big part of what HDYO was doing.'

When the pandemic first started in 2020 and pretty much the whole world was in lockdown, we were doing a lot virtually, like weekly support groups and all kinds of things, just to get young people engaged. But you can only have so much of those things, I think, and then it kind of gets a bit dry.

You mentioned the isolation that younger people affected by HD can experience. Could you tell me about the further effects of lockdown and all the other COVID restrictions on young people?

I think at first, the whole COVID thing was very distracting. It just took over everything for a few months and what we tended to see was actually a slight dip in the numbers of people contacting us for support. I think young people weren't really thinking as much about their risk at that time or whether they wanted to get tested, so we weren't getting the usual questions about genetics and things like that.

So, will you be having an in-person meeting next year?

Yes! Our international Young Adults Congress will be held in person on **17–19 March 2023 in Glasgow, Scotland.** This event is designed for young adults, families and professionals (more details can be found at https://hdyocongress.org/). We're also going to be doing camps in different regions and reaching out to young people who don't get a lot of opportunities for support.

And finally, what else is on the horizon for you?

Excitingly, we recently hired a new Executive Director – Jenna Heilman. She's been working with us for about 11 months or so, and we also have a few new team members and board members as well. So, people are getting settled in but one of the things that we have recently started is Join-HD (see our update from Jenna Heilman in this edition for more on this).

We're also working on mentorship in the USA. This is an initiative that was very popular in Canada, whereby, essentially, we pair a young person with another slightly older young person who has experience that might be valuable to share. The two young people can connect and can also be guided by other professionals, such as social workers. This initiative has a lot of potential, and maybe in the future, could become global. We shall see what the future holds!

HDYO
HUNTINGTON'S DISEASE YOUTH ORGANIZATION

Website: https://en.hdyo.org/
Youtube: https://www.youtube.com/user/HDYOFeed
Twitter: @HDYOFeed
Email: info@hdyo.org

Gerrit Dommerholt: A Tribute

Asun Martinez and James Pollard,
Asociación Jóvenes Huntington

Gerrit Dommerholt

Gerrit Dommerholt passed away aged 85 years on New Year's Eve 2021. A retired Dutch military officer and member of an HD-affected family, he is perhaps best known for his leading role in founding the Dutch, European and International Huntington's Association (IHA). He was IHA President between 1989 and 1993, and for many years after, travelled the globe as the IHA Development Officer.

When a single family member in a country contacted him for help, Gerrit would ask, 'If you want to help one family in your country, why not help them all.' HD associations have now spread across five continents, a credit to Gerrit's early collaboration – an integral part of their growth and success. He used wisdom collected from the founding of other associations to show founders how to reach other HD families in their countries, how to bring them together in an era when stigma was a significant impediment to initial meetings, and to alert them to the practical challenges of managing the issues encountered by new associations.

The unique partnership that families and scientists share today can be traced directly to Gerrit's early guidance and his insistence that families be full partners in our collective quest for an effective treatment. As a driving force in our international movement, his decades of hard work, collaboration and activism continue to inspire both families and professionals. Rest now, Gerrit. Together, we continue your work.

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Follow us on Twitter:
@EHDN_*News*

Dates for your diary

EHDN 2022 Bologna 16-18Sep

- **The EHDN Plenary Meeting** will take place in Bologna, Italy, 16–18 September 2022. The programme (PDF) is available at www.ehdn.org/ehdn2022/, registration is open until 22 July 2022. Click here to register or email ehdn2022@euro-hd.net with any questions.
- An online networking event **'Biophysics of polyglutamine aggregation: How does it start and how does it end?'** will take place via Zoom on 6 July 2022. For more information and to register click here.
- Registration is opening soon for the **Huntington Study Group 2022 Annual Meeting** which will take place in Tampa, Florida, 3–5 November 2022. Further details are available here.
- STOP PRESS!! The **HDYO Congress** for young adults, families and professionals impacted by HD will be held in person, March 17–19 2023, in Glasgow, Scotland. For the latest updates visit https://hdyocongress.org/

Would you like to share an upcoming event with our readers?
Please email the details to newsletter@euro-hd.net