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EHDN News

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

Photos: Gabriele Stautner · artifox.com

A warm welcome was extended to all

EHDN2022

PHOTOS RECORDINGS REPORT

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EHDN2022: Inspiring Progress, Fuelling Hope

Catherine Deeprose

Almost 1,000 delegates convened in Italy's lively and historic city of Bologna for EHDN 2022 – our first face-to-face plenary meeting after the COVID-19 hiatus. After the challenges of the pandemic and disappointments in recent clinical trials, we welcomed faces old and new in coming together to discuss updates, ideas and experiences with the shared vision of inspiring progress in HD research. Here is a whistlestop tour of the many highlights of the event.

Charlotte Raven

150 Years of Huntington's Disease

The opening Keynote Session commenced with speaker **Charlotte Raven**, British journalist and author of 'Patient 1: Forgetting and Finding Myself' who shared a personal and poignant account of her journey, including being the first patient to receive tominersen and her pride in being part of the search for a cure. Next to

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Catherine Deeprose, Editor
Gabriele Stautner Artifox Communication Design (Ulm, Germany).

Gillian Bates

Elena Cattaneo

speak was **Gillian Bates**, Professor of Molecular Neuroscience at University College London, with a critical review of cytosine, adenine and guanine (CAG) repeat size in HD and some of her fascinating work informing both theory and methodological approaches in the search for therapeutic targets.

Elena Cattaneo,Professor of Pharmacology, at the University of Milan, addressed the the big issues – the biology of the origin of life as it relates to HD pathology, describing how with the progression of evolution, we see an increase in CAG size associated with species with progressively more advanced nervous systems.

In Memory of Professor Lesley Jones (1957–2022)

With sadness, **Anne Rosser and Sarah Tabrizi** (University College London) paid tribute to our friend and colleague, Lesley Jones, who passed away in June this year. We heard how Lesley spent most of her professional life at Cardiff University, where she completed her first degree and PhD before being appointed as a scientist and lecturer, and then in 2012, Professor in Neuropsychiatric Genetics. Having started her career working across several neurodegenerative diseases, she increasingly focussed on HD, for which she is now best known. With a range of collaborators across the globe, Lesley was central to the activities of the Genetic Modifiers of Huntington's Disease Consortium and was a world leader in the explanation of HD gene modifiers. At the time of her death, Lesley was a core member of the EHDN Executive Committee and Think Tank, and her contributions in these roles were characterised by energy and engagement. Lesley made immense contributions to our understanding of HD at every level and published critical papers that will remain highly influential in the field. She worked across cell biology, mouse behaviour and the genetics of HD, pioneering efforts that are resulting in new therapeutic targets and possibly new treatments. Lesley is also known for making huge contributions to our understanding of Alzheimer's disease, being among the first to recognise the central role of Glial cells in its pathogenesis. A much-loved and respected figure, Lesley was well known for her sharp intellect, good sense and kindness, and in particular, her careful attention to the needs of young scientists and strong support of women in science. She also cared deeply about patients and families. We have lost a good friend, a supporter and a truly remarkable woman whose inspiration will be carried into the future with our new generations of scientists.

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Keynote Lecture: Lessons Learnt from Other Neurodegenerative Disorders

Dieter Edbauer, Professor of Translational Neurobiochemistry at the German Center for Neurodegenerative Diseases, presented 'Vaccines and Small Molecules to Target Dipeptide Repeat Proteins in C9orf72 ALS (Amyotrophic Lateral Sclerosis)/FTD (Frontotemporal Dementia)'. ALS and FTD are both neurodegenerative diseases and though present quite differently clinically, they share the common mutation of the repeat expansion in the C9orf72 gene. Edbauer described his elegant work dissecting C9orf72, and highlighted the role of repeat-associated non-AUG translation in causing neurodegenerative diseases such as ALS and FTD, and also HD. These new insights into ALS and FTD disease pathology are informing several avenues of intervention which are currently in development.

Dieter Edbauer

Keynote Lecture: HD-Integrated Staging System – A Primer for Use in Clinical Research

Sarah Tabrizi

Sarah Tabrizi, Professor of Clinical Neurology & Neurogenetics at University College London, opened with the broader context of medical staging systems before explaining the development of the Huntington's Disease Integrated Staging System (HD-ISS) by the Critical Path Institute HD-Regulatory Science Consortium Working Group. We heard that with the HD-ISS, HD is still defined by genetic testing but disease progression is classified into four Stages (0, 1, 2, 3), covering the entire lifespan and creating a framework for intervention before clinical motor diagnosis. While there are many advantages to using the HD-ISS in clinical research, Tabrizi explained that ultimately, it paves the way for trials and treatments earlier in the progression of HD with the hope to prevent or delay disease progression.

Special Report: Towards an Understanding of the Posttreatment and Mechanistic Aspects of Tominersen

Peter McColgan

Roche's **Peter McColgan** delivered this special report which delved into further detail on GENERATION HD1 now the final study visits and further analyses have been completed. McColgan explained that the initial increases in the rate of ventricular volume increase with tominersen seen at 37 weeks decreased at later time points and post-treatment. In addition, we heard that further analyses showed that rates of disease progression in the post-treatment period did not differ between tominersen and placebo. Mechanistic studies have led Roche to believe that lower doses of tominersen may mitigate unwanted effects such as ventricular volume increase.

Photos: Gabriele Stautner · artifox.com

Nora Guthrie

Special Lecture: Nora Guthrie

The first day of the 2022 plenary meeting was brought to a fitting close with the highly anticipated and equally well-received Special Lecture by the enigmatic Nora Guthrie (see also our interview at the end of this issue). After a busy day of science and statistics, we enjoyed listening to her hugely inspiring reflections and account of a family affected by HD accompanied by stunning visuals including photographs and videos, and of course, music.

Plenary Sessions

Darren Monckton

Larissa Arning

Joseph Hamilton

Galen Wright

Tess Persson

In the first plenary on the new genetics of HD, **Darren Monckton** (University of Glasgow) reminded us of the value of human genetics and the need to study diverse human populations in elucidating HD biology. **Larissa Arning** (Ruhr University Bochum) focussed on the neurodevelopmental hypothesis of HD which suggests that the CAG repeat-expansion is the pathological extreme of a more general mutational process contributing to normal brain function and development. Remaining on the theme of CAG repeat length, **Joseph Hamilton** (University College London) spoke on FAN1 as a genetic modifier in HD and proposed new therapeutic targets for preventing the expansion of the CAG repeat. **Galen Wright** (University of Manitoba) concluded with his presentation of HD as a case study to illustrate the power of human genetics research, citing key studies and highlighting new avenues for therapeutic development.

The second plenary looked at approaches to quality of life and the clinical management of HD, starting with a presentation by **Tess Persson** who discussed the cognitive, mental and physical challenges she had experienced, and shared insights into the approaches she has found


B. Landwehrmeyer


Åsa Petersén


Duncan McLauchlan


Michael Hayden


Ricardo Dolmetsch

helpful. She was followed by **Bernhard Landwehrmeyer** (Ulm University), speaking on behalf of Stephen McKenna (Galen Research) on the development of a new HD-specific measure of quality of life. **Åsa Petersén** of Lund University in Sweden took a different perspective in discussing the emotional and psychiatric aspects of HD, concluding that more research and better therapies are still needed. **Duncan McLauchlan** (Cardiff University) remained on this topic, asking whether HD pathology contributes to psychiatric disorders, and presented the example of depression.

The third plenary session provided an eagerly anticipated update on ongoing clinical trials. **Michael Hayden** of **Prilenia**, updated on the phase 3 PRidopidine Outcome On Function in Huntington Disease (PROOF-HD) study. We heard that the FDA has now granted fast-track designation for pridopidine and study results are anticipated in early 2023.
Ricardo Dolmetsch of **UniQure**, explained that in a phase 1/2 study (USA) and an open-label trial (Europe), the low dose of AMT-30 [which targets exon-1 of the huntingtin (HTT) gene] continues to be


Danlin Xu


Amy-Lee Bredlau


Catherine Scart


Irina Antonijevic

well tolerated but the high dose is on hold pending safety review. Next to speak was **Danlin Xu** of **Wave Life Sciences**. WVE-003 was designed selectively lower mutant (m)HTT and is under investigation in SELECT-HD, a phase 1b/2a trial in which the activation of sites and recruitment are ongoing. **Amy-Lee Bredlau** of **PTC Therapeutics**, discussed PTC518, an orally available pre-mRNA splicing modifier that lowers HTT in HD mice and shows mRNA and protein lowering in healthy volunteers. The PIVOT-HD phase 2 study started in early 2022 and is looking at safety and efficacy in HD. **Catherine Scart** of **SOM Biotech**, told us that the expected benefits for SOM3355 (bevantolol hydrochloride, a vesicular monoamine transporter 2 inhibitor) were confirmed in a phase 2a proof of concept study and their phase 2b study is expected to complete in 2023.
Irina Antonijevic of **Triplet Therapeutics**, presented on their antisense oligonucleotide (ASO) approach and the rapid development of TTX-3360. Triplet has several backup molecules with improved characteristics and is looking for a partner to support the ASO programme.

Romina Aron-Badin

Liam Gray

Cheney Drew

Anne Rosser

Jan Vesper

The fourth plenary was on advanced therapies and held on the last day of the meeting. **Romina Aron-Badin** (French Alternative Energies and Atomic Energy Commission) provided an introduction and overview of the challenges of delivering advanced therapies to the brain, including difficulties in bypassing the blood-brain barrier. **Liam Gray** (Cardiff University) noted that while direct delivery of therapeutics to the brain has specific advantages, it also comes with significant challenges, including accuracy and access in the pathological brain. Gray also introduced the newly established EHDN Surgical Delivery Task Force and outlined their next steps. **Cheney Drew** (Cardiff University) presented an overview of the alternatives to the 'gold standard' of randomised controlled trial in clinical research and called on researchers to engage with the full breadth of the HD community to find ways to deal with the inherent challenges in this. **Anne Rosser** presented on recent developments (and challenges) in cell therapies, provided updates on several human ES derived neural progenitor studies, and concluded with a discussion on using HD as a model for translating cell therapies for neurodegenerative diseases. Last to speak was **Jan Vesper** (Heinrich Heine University Medical Center) who took a slightly different approach in his presentation on deep brain stimulation (DBS) in HD, in which he concluded that pursuing DBS as a treatment at the current time is unsupported.

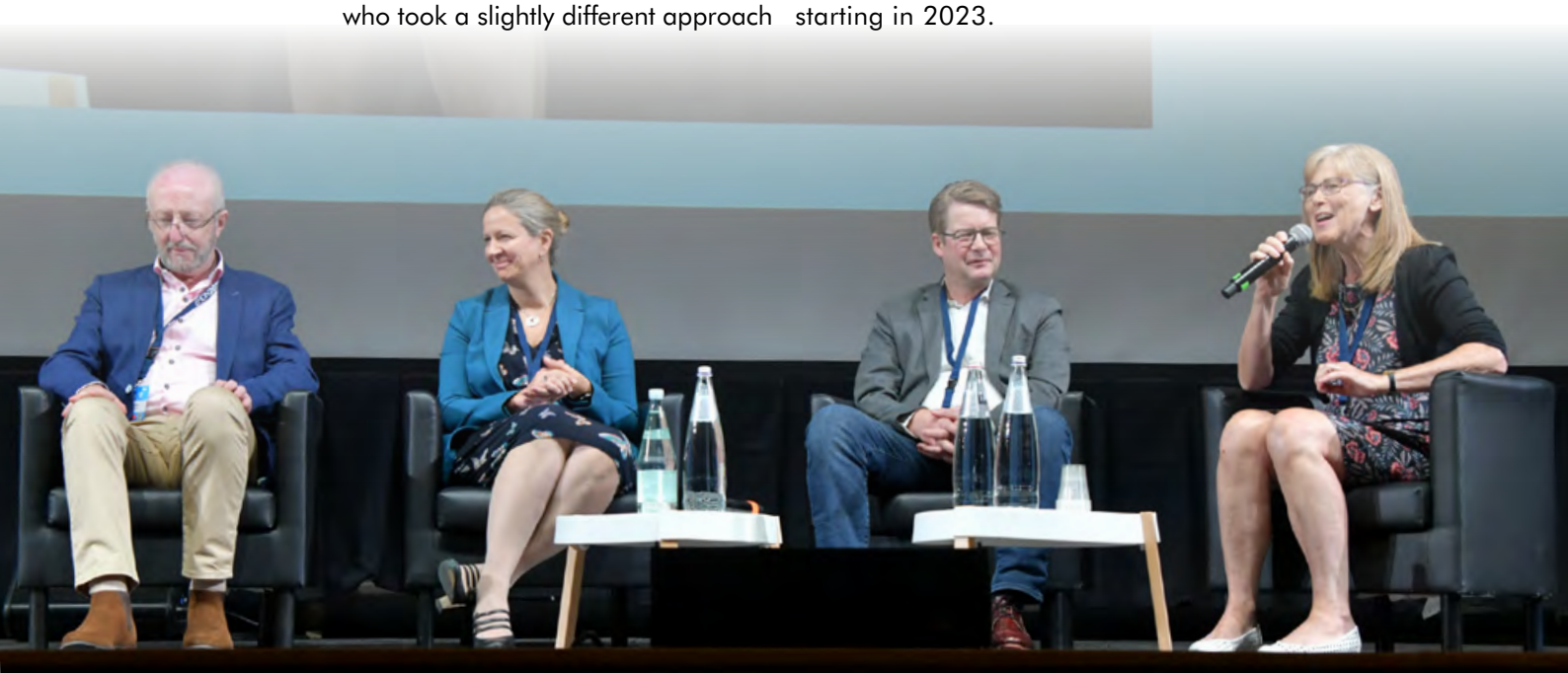
Nathalie Cartier-Lacave

Aaron Koenig

Peter McColgan

Henk-André Kroon

The final plenary session provided an update on upcoming clinical trials. **Nathalie Cartier-Lacave** of **AskBio** presented on restoring brain cholesterol metabolism in HD using gene therapy. BV-101, an adeno-associated virus gene therapy that encodes CYP46A1, is currently being evaluated in an open-label phase 1/2 dose-finding study. **Aaron Koenig** of **Sage Therapeutics** discussed targetting cognitive impairment with SAGE-718, a novel, investigational NMDA receptor positive allosteric modulator in their PERSPECTIVE programme. **Peter McColgan** of **Roche** then announced GENERATION HD2 – a new phase 2 dose-finding study of tominersen (100 mg or 60 mg every four months compared with placebo) which will evaluate safety, biomarkers and clinical efficacy trends. The last speaker was **Henk-André Kroon** of **Annexon Biosciences** and we heard that in a small phase 2 study, ANX005 (a monoclonal antibody that inhibits C1q) showed C1q target engagement in blood and cerebral spinal fluid (CSF), clinical improvement and decreased neuroinflammation. Findings will be confirmed in a larger, placebo-controlled clinical study starting in 2023.



Parallel Sessions

Stefan Kochanek

Frédéric Saudou

Hilal Lashuel

Marcus D'Souza

Jonas Dorn

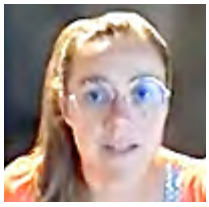
The first parallel session was dedicated to the understanding of HTT structure and function. **Stefan Kochanek** (Ulm University) built on earlier discussions on different disease mechanisms and he explained his current focus on HTT and huntingtin-associated protein 40 and their interaction. Next to speak was **Frédéric Saudou**, who described how huntingtin is involved in vesicular transport along microtubules and is altered in disease, and the potential for the cortex, and in particular, axonal transport for HD therapeutic intervention. The final speaker here was **Hilal Lashuel** (Swiss Federal Institute of Technology Lausanne) who discussed the mechanisms of HTT aggregation and proposed that inclusion formation is the missing link in our understanding of HD.

Meanwhile, a concurrent session focussed on digital endpoints was opened by **Marcus D'Souza** (University Hospital Basel), who presented on bridging from multiple sclerosis to HD in the capture and documentation of clinical measures, including the HD-ISS. **Jonas Dorn** (Roche) followed with the Roche HD digital monitoring platform (dMP) which has been used as part of the tominersen development programme. We heard that this may capture disease progression earlier and more sensitively than the composite Unified Huntington's Disease Rating Scale (UHDRS) score. Finally, **Robin Schubert** (George Huntington Institute) discussed the digital Q-Motor system which quantitatively assesses motor function and also cognition (Q-Cog) and presented data from different studies (PRIDE-HD, LEGATO-HD and AMARYLLIS) in which Q-Motor showed greater sensitivity than the UHDRS–Total Motor Score.

Robin Schubert

Henrik Zetterberg

Douglas Macdonald



Aline Delva

A further parallel session examined the use of biomarkers in clinical trials of neurodegenerative disorders. **Henrik Zetterberg** (University of Gothenburg and University College London) provided a brief history of the association between the neurofilament protein in CSF and neurodegenerative diseases, including HD, and the implications of this for current research. **Douglas Macdonald** (CHDI Foundation) described the development of CHDI_HTT_143 which selectively measures total huntingtin (wildtype HTT and mHTT combined) and presented data supporting the sensitivity and validity of this assay. **Aline Delva** (University Hospitals, Leuven/KU Leuven) then presented an update on iMAGEmHTT, reporting data showing that 11C-CHDI-180R is a promising PET radioligand in targeting mHTT aggregates.


Mariacristina Capizzi


Radhia Kacher


Ferdinando Squitieri


Mahmoud Pouladi


Sanaz Gabery

The parallel session on neurodevelopment in HD and paediatric/juvenile HD was opened by **Mariacristina Capizzi** (University Grenoble Alpes), who explained that although HD is considered an adult disorder, the mutated protein is expressed from the foetal stage and she presented studies illustrating disorganisation of the microtubule cytoskeleton during development in HD. Then, **Radhia Kacher** (Paris Brain Institute) presented long-term data from HD participants apart as well as foetal and post-mortem data which, taken together, showed that CAG somatic expansion increases in HD throughout the lifespan. Finally, **Ferdinando Squitieri** (LIRH Foundation and CSS-Mendel Institute) argued that research should identify the factors contributing to the more severe progression seen with younger onset of HD, and that this should go beyond the nervous system.

White matter changes in HD formed the focus for another parallel session in which **Mahmoud Pouladi** (University of British Columbia) described work showing how different forms of myelination are altered in HD and he proposed that oligodendroglial dysfunction contributes to white matter and myelination abnormalities and other neurological manifestations. **Sanaz Gabery** (Lund University) pointed to the psychiatric symptoms that can appear early in the progression of HD, and proposed that the limbic system and in particular, the fornix, may be involved. Following on from this, **Anna Williams** and **Sunniva Bøstrand** (both University of Edinburgh) described their work on understanding and manipulating myelin pathology, and in particular, the therapeutic potential of glia.


Anna Williams


Sunniva Bøstrand


Ruth Veenhuizen


Una Jones


Manon van Kampen


Margret Knoll

In the parallel session on multidisciplinary care, **Ruth Veenhuizen** (Atlant and Amsterdam University Medical Center) discussed the use of moral case deliberation in HD care. This approach is argued to enhance proficiency, professional collaboration and quality of care. She was followed by **Una Jones** (Cardiff University), who discussed how a person-centred approach to goal setting, the development of individualised plans and specific physiotherapy expertise can facilitate physical activity in HD. **Manon van Kampen** (Atlant) discussed practical tips for guiding the transition from independence in daily living and also speaking from Atlant was **Margret Knoll** on nutrition decision-making, who had a specific focus on individuals for whom oral nutrition is no longer possible or safe due to challenges in eating and drinking.

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EHDN Business Meeting

Anne Rosser and Patrick Weydt conducted this important component of the plenary meeting. Members of the existing Scientific and Advisory Board (SBAC) and the Executive Committee (EC) had agreed to extend the duration of their positions over the COVID pandemic to the current election. In a change from previous elections, a slate of SBAC candidates had been proposed to ensure appropriate cover of important areas of excellence and expertise. Thanks were given to the members stepping down, namely, Kathrin Reetz, Kristina Bečanović, Esther Cubo, Leonor Correia Guedes, Paola Bellosta, Jennifer Hoblyn, Katrin Lindenberg, Karine Merienne, Saul Martinez-Horta, Martha Nance and Daniel Zielonka. Ahmad Aziz will continue to chair the SBAC to provide continuity, and incoming members Sandrine Betuing, Marta Biagioli, Silvia Gines, Davina Hensman Moss, Jiří Klempíř, Duncan McLauchlan, Hoa Huu Phuc Nguyen, Mayke Oosterloo, Willeke van Roon-Mom, Niels Henning Skotte and Chiara Zuccato were extended a very warm welcome. The patient representative, statistics advisor and ethics advisor (Dina de Sousa, Peter Holmans and Heidi Bentzen, respectively) are appointed through a separate process. Dina de Sousa is now the European Huntington Association's appointed member to the EC. The appointed members (Peter Holmans and Heidi Bentzen) will remain at the current time and Dina de Sousa is now the European Huntington Association's appointed member to the EC. Moving on to the EC, Ralf Reilmann, Raymond Roos and Sandrine Humbert received thanks for their contributions and then the election results were announced. Patrick Weydt was re-elected and newly elected members Åsa Petersén, Monica Busse and Ed Wild each introduced themselves on stage and shared their vision for working with the EHDN. Kathrin Reetz, previously the SBAC Chair, was also elected to the EC but could not be present.

Rosser then reviewed the criteria that clinical trials must adhere to be endorsed by the EHDN and illustrated the range of studies that have been endorsed since 2018. She also reviewed data mining and seed fund applications. Since 2018, 12 Registry data mining applications were approved and 139 seed fund applications were made with 20 being awarded. The seed fund programme has been renamed to honour Professor Lesley Jones and applications can be made in March and November each year. The Think Tank assists the EC and interacts with WGs and TFs and inputs into the fellowship programme but is also available for discussions with EHDN members upon request. Recent initiatives include the Digital Assessments in HD WG, Advanced Therapies Surgical WG, Dysphagia TF and Incidental Findings TF. Areas of special focus over the past few years include imaging and quality of life.

We were reminded that the objective of the Fellowship Programme is to provide clinical multidisciplinary training in HD to young professionals currently working in underserved areas. This is offered in collaboration with the International Parkinson and Movement Disorder Society

– European Section (MDS-ES) and typically six places are available each year. While the programme was paused in 2021 and 2022 due to COVID-19, the plans to resume in 2023 are nearly complete and the deadline and process for applications (January/February 2023) will be finalised shortly. Updates will be provided on the EHDN website.

Other activities include the continued development of the site certification scheme, EHDN/MDS training webinars, a virtual platform to discuss the Roche study, and the development of a new scientific strategic plan (previous plans had been made in 2011 and 2017). Development of the strategic plan is currently underway and this is intended to run from 2023 for 4–5 years. More updates on this will be available soon!

Finally, thanks were given to all those working behind the scenes to support this work, and in particular, the EHDN Central Coordination team, the Ulm 'container' office (led by Bernhard Landwehrmeyer) and CHDI for funding.

What do Results from Clinical Trials Mean?

Chairs Jean-Marc Burgunder and Patrick Weydt were joined by Henrik Zetterberg, Bernhard Landwehrmeyer, Jessica Koehli, Anne Rosser, Peter McColgan and Irina Antonijevic for a round table discussion. Questions were also invited from the audience and stimulating discussions emerged on several topics, including the importance of converging evidence from different biomarkers in clinical trials, discussion about what has been learned from recent studies and also the importance of meetings such as these in providing a forum to advance the HD field.

Photos: Gabriele Stautner · artifox.com

Almost 300 posters had been on display

Poster Awards

Åsa Petersén announced the poster awards presented in honour of Lesley Jones. The awardees were Maximilian Wagner of Ulm University, Germany, Laura Heraty of Cardiff University, UK, and Laurent Cotter of the French Alternative Energies and Atomic Energy Commission, Molecular Imaging Research Center, France.



Photos: Gabriele 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.

The studies reported below are of investigational compounds, where the safety and efficacy have not been established. There is no guarantee that the outcome of these studies will result in marketing approval.

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.

ASK-HD-01-CS-101 (Asklepios Biopharmaceutical, Inc. [AskBio])

This open-label phase I/II study will evaluate the safety and efficacy of BV-101, a novel gene therapy targeting cholesterol metabolism dysfunction. BV-101 delivers the enzyme CYP46A1, which is reduced in people with HD, and aims to restore cholesterol metabolism, reduce mutant huntingtin (without affecting the levels of normal huntingtin) and improve neuronal function. Preclinical studies in mice have demonstrated that BV-101 can repair the cholesterol pathway, restore motor performance, reduce mutant huntingtin aggregates, and provide neuronal protection. The study will enrol up to 18 participants, each of whom will receive BV-101 via a one-time intracerebral bilateral injection. The study is anticipated to start in Q4 2022.

VIBRANT-HD (Novartis)

Dosing in this phase IIb study of orally administered branaplam was temporarily paused in August, as signs of side-effects (peripheral neuropathy) were detected in some participants following a routine data safety review by the independent Data Monitoring Committee. Importantly, the study is continuing to follow participants with the planned assessments and visits, so more data and information can be gathered to better understand these side-effects and to determine the next steps.

SOMCT03 (SOM Biotech)

Recruitment has started into this European phase IIb safety and efficacy study of orally administered SOM3355 (bevantolol hydrochloride), a VMAT2 inhibitor. SOM3355 is anticipated to have fewer side effects than existing treatments of chorea based on the drug's existing profile.

SAGE-718 (Sage Therapeutics)

Two phase II trials have been initiated to assess the effect of an orally administered novel oxysterol-based NMDA receptor modulator, SAGE-718, on cognitive performance and functioning. The trials will use several cognitive assessments, standard HD rating scales and assess safety and tolerability of the drug. DIMENSION-HD will evaluate the efficacy of SAGE-718 compared with placebo in participants with HD when administered over 3 months and will be performed at approximately 50 sites in Australia, Europe and North America. A smaller study called SURVEYOR-HD will be performed at up to 10 sites in North America only and will recruit participants with HD and healthy volunteers, with the aim of gathering evidence to test the effect of the drug on cognitive performance and the ability to perform real-world tasks assessing function when administered over 28 days.

HDGeneTRX1 and HDGeneTRX2 (UniQure)

Dosing is continuing for the AMT-130 studies. In July, the company reported to regulators that there were three suspected unexpected severe adverse reactions

(SUSARs) in participants that received the higher dose (two participants in the EU and one in the US). Two participants reported inflammation and one participant experienced severe headache 1–2 weeks following administration. The participants have now completely or largely recovered and have been discharged from hospital. Currently, these SUSARs are not viewed as dose-limiting toxicity by the trial Data Safety Monitoring Board, but enrolment into the higher-dose group is suspended pending a full safety review planned early in Q4 2022. The first 12-month data for the lower dose group treated in the US study were reported in June. Levels of mHTT were reduced by up to 53.8% (N = 4) in CSF at 12 months vs. baseline and were lower than the mHTT levels in the control group (16.8%, N = 3). These data are encouraging despite the small numbers in each group.

PIVOT-HD (PTC Therapeutics)
Recruitment has started in North America for this phase IIa study of orally administered PTC518 (a small molecule huntingtin lowering compound). Further sites in North America, Australia and Europe are expected to be activated over the coming months. The first data are anticipated by the end of 2022.

SELECT-HD (Wave Life Sciences)
Following a recent DSMC review, the study will continue recruitment into the highest of the three planned single-dose cohorts and will be expanding the cohorts to gather more data to inform the optimisation of dose level. In September, Wave reported preliminary data showing that single doses of WVE-003 reduced mHTT in CSF by 22% across the first two dose cohorts examined, and that these doses appear safe and well-tolerated. Levels of normal HTT were consistent with selective reduction of mHTT, indicating that the drug is allele selective. The next data review is expected in 1H2023.

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
NCT05541627	BrainVectis, a subsidiary of Asklepios BioPharmaceutical, Inc. (AskBio)	ASK-HD-01-CS-101	I/II	BV-101	Cholesterol metabolism dysfunction (AAV gene therapy)	18	France	Start-up
N/A	Cardiff University	DOMINO-HD	N/A	N/A	N/A	300	Poland, Spain, Switzerland, UK	Participant follow-up
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
NCT05107128	Sage Therapeutics	DIMENSION-HD	II	SAGE-718	NMDA receptor modulator	178	Australia, Europe, North America	Recruiting
NCT05358821	Sage Therapeutics	SURVEYOR-HD	II	SAGE-718	NMDA receptor modulator	80	North America	Recruiting
NCT05475483	SOM Biotech	SOMCT03	IIb	SOM3355/ bevantolol	VMAT2 inhibition	129	France, Germany, Italy, Poland, Spain, Switzerland, UK	Recruiting
NCT04406636	Triplet Therapeutics	SHIELD-HD	N/A	N/A	N/A	60	USA, Canada, Europe	Participant follow-up
NCT04120493	UniQure	HD GeneTRX2	Ib/II	rAAV5-miHTT	miRNA nonselective (AAV 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

AAV = adeno-associated virus; ASO = antisense oligonucleotide; OLE = open label extension; VMAT2 = vesicular monoamine transporter 2

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Photos: Gabriele Stautner · artifox.com

Update: Sixth Enroll-HD Periodic Dataset is Coming Soon!

Olivia Handley, Enroll-HD Global Platform Manager

As Enroll-HD celebrates its 10-year anniversary since recruiting its first participant, we are delighted to announce the next Enroll-HD Periodic Dataset (PDS) will be available by the end of this year.

The Enroll-HD PDS will be the sixth release and will provide the largest dataset yet from the Enroll-HD study. Planning and delivering the dataset is no mean feat – with over 60 million data points and close to 90,000 study visits, it takes a small army of people to review, clean, prepare, check, recheck, and package up the data.

The Enroll-HD PDS is recognised as being a high-quality, robust dataset, and ensuring this is maintained requires considerable effort. First, each site is carefully trained to promote the standardised administration of assessments and to submit study data to a central electronic data capture (EDC) system. The EDC contains hundreds of checks to make sure data values are plausible and accurate. Data entry values that deviate from what the system expects are automatically flagged (e.g., a height value of 15 cm would generate an error message), and missing data require an explanatory comment (e.g., the reason for missing cognitive scores). Once a site has electronically signed off the data, a dedicated biostatistics and remote monitoring team conduct routine quality control checks by running complex queries on periodic data exports, flagging unusual values that may require follow-up with a site. Once data have successfully passed through this remote review, Enroll-HD monitors are deployed to carry out onsite monitoring visits to each site. Larger sites may be visited up to five times a year, and every site is visited at least once a year. Onsite monitoring follows a risk-based approach which means not every piece of data is checked, rather, certain data are either 100% (informed consent verification), or 50%, 25% or 10% checked (e.g., paper cognitive tests reviewed to confirm correct administration and accurate transcription). There are also data that are not onsite checked; this is because they have successfully passed the remote data review process and are considered 'clean'.

Once data have completed the monitoring process, each participant

Photo: Gabriele Stautner · artifox.com

Ruth Fulham and Selene Capodarca celebrating Enroll-HD being 'Ten years strong' at the EHDN2022 in Bologna

and their visits are checked against set criteria for PDS data inclusion. For example, the PDS will only include participants who have had their Enroll-HD informed consent form verified and each confirmation of research CAG genotyping and completed coding of comorbidities, as well as other criteria. When these rules are applied, there is inevitably a drop-off of participants and/or visits. Since we aim to include as many participants and visits as possible, it's important for the PDS team to run these checks at least 6 months in advance of the release, identify which data needs to be coded, which informed consent forms should be checked and so on, to maximise the amount of data that can be included.

The curation of the final PDS requires the team to carefully extract the data and run a series of checks to make sure the data are accurate and to ensure the risk of identification is acceptable. One approach to minimise the risk of identification might be to aggregate values, for example, a larger allele CAG length of 88 might be aggregated into a '>71 CAG' group, since having a very long CAG length of 88 could be potentially identifying. Supporting documentation for end users is carefully reviewed ahead of each release, ensuring that data handling guidelines, exceptional value statements, data dictionaries, and annotated case report forms are all accurate and complementary to how the data can be exported, manipulated, and interpreted.

Access to the Enroll-HD PDS can be given to a researcher at a recognised research organisation. There must be an institutional authorisation to sign the data use agreement and requestors are required to submit a completed data security questionnaire and a detailed description of the organisational IT security measures.

We do not yet know the final number of participants and visits to be included in this version of the PDS. However, it will certainly be bigger and better than its predecessors. And that is an important aspect of the platform – as it continues to thrive and expand, so too do the outputs that can be fed directly back into the research community.

For more information on how to access the Enroll-HD PDS, please visit: https://enroll-hd.org/for-researchers/access-data-biosamples/

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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

Photo provided by Kristina Bečanović

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

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 high-quality CSF collection and plasma samples (from blood) to evaluate biomarkers and pathways to enable the development of novel treatments for HD**
- **Collect high-quality clinical data for each participant using Enroll-HD core assessments**

All HDClarity participants must be part of the ENROLL-HD study and HDClarity is aiming to recruit 2,500 participants worldwide. Since 2016, the study has opened across seven nations worldwide and has over 500 participants.

Our current and actively recruiting sites are located across the UK, Canada, USA, Germany, Italy, Poland and Spain. Recently, the study was opened in new sites within Great Britain, USA and Germany and we are close to opening the study in Australia and New Zealand. Across all of the currently active sites, Germany continues to be the highest recruiting country for HDClarity (Figure 1).

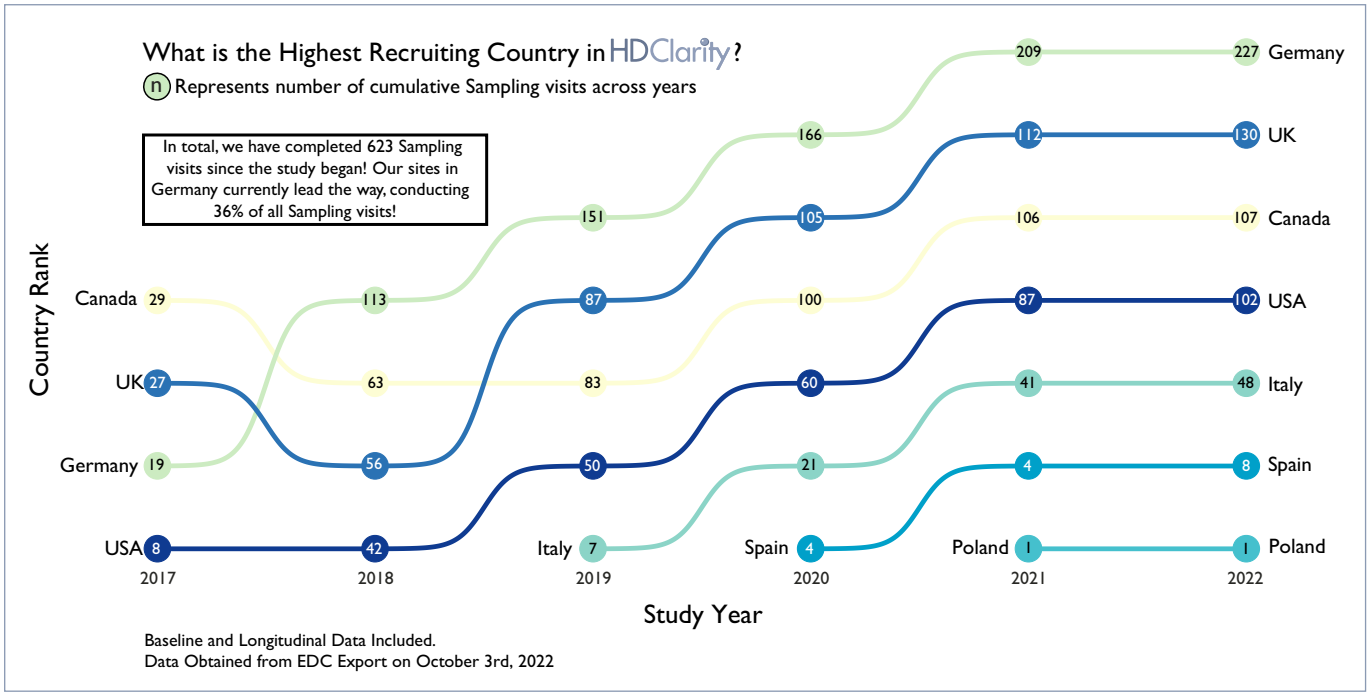


Figure 1. HDClarity Recruitment by Country (as of October 2022)

Total Recruitment

As of October 2022, 623 CSF and plasma sampling visits have been conducted. Across all study years, our highest recruiting participant category has been **Early HD,** accounting for over **35%** of the total sampling visits (Figure 2).

The 'Incomplete Penetrance' category has been introduced as part of Protocol v4, along with 'Juvenile HD' and 'Uncategorised'

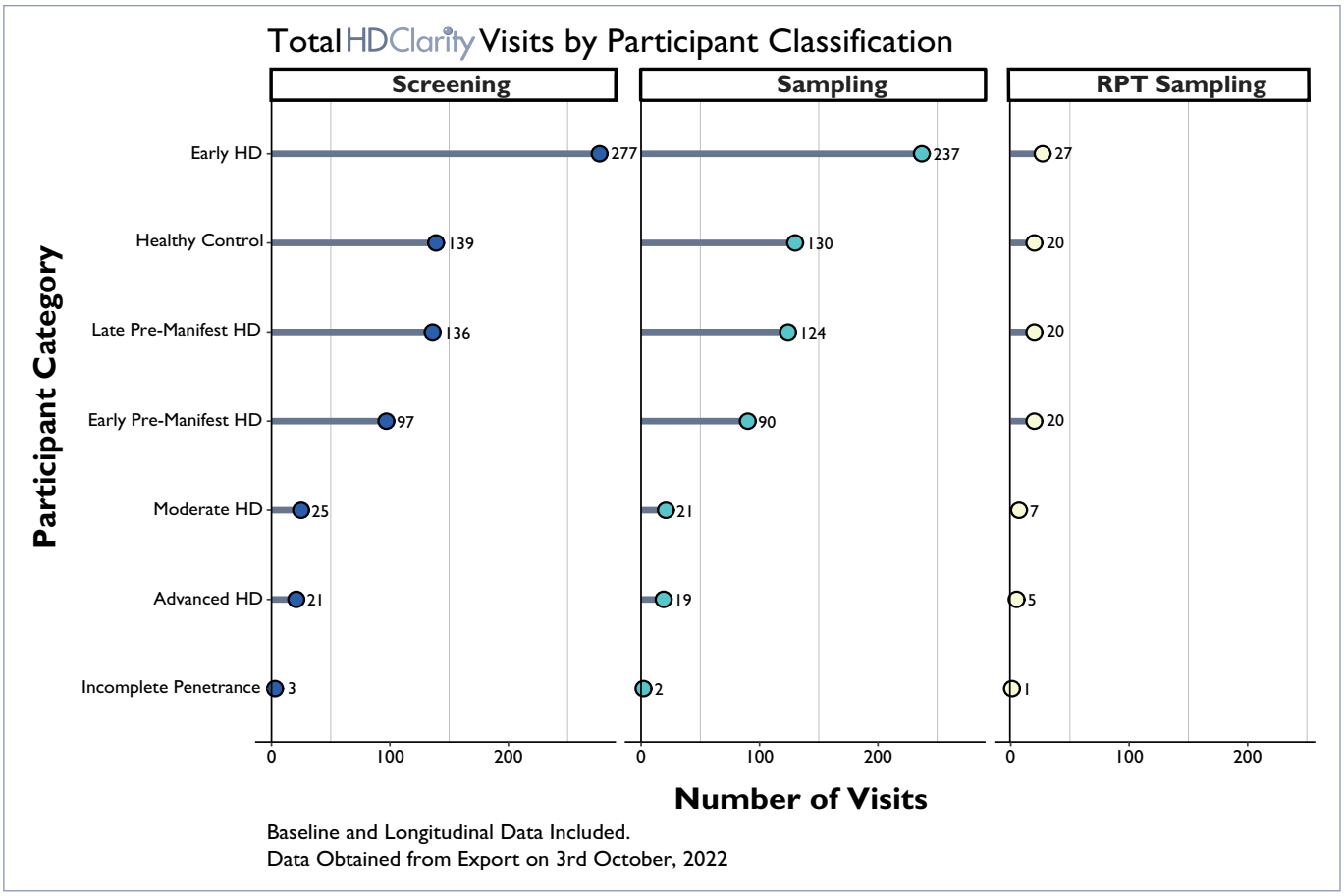


Figure 2. Total HDClarity Visits by Participant Classification (as of October 2022)

Longitudinal Visits

The introduction of **Protocol Version 4** 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 the majority of HDClarity UK sites can recruit participants under the new version of Protocol V4 (Figure 3) and we are currently aiming to transition all active UK sites all active UK sites including Plymouth Hospital NHS Trust and Oxford University Hospital Trust to the new version of the protocol.

Research:

Participants in HDClarity will be asked to donate 20 ml of CSF via a lumbar puncture (using local anaesthetic if required) and 50 ml of blood by venepuncture. Some participants will be invited to attend a repeat optional sampling visit 4–6 after the first sampling visit for the first year of recruitment only. After collection of CSF and plasma (from the blood samples), the samples are sent to a specialist laboratory in Milan, Italy. From here scientists, research institutes and doctors can request these samples for further investigations. To date, these samples have already been requested by research groups across the world to investigate potential new biomarkers and proteins and to provide valuable information and further insights into how the nervous system is affected by HD.

Sites Name
Royal Devon and Exeter NHS Foundation Trust
University College London Hospitals NHS Foundation Trust
University Hospitals Birmingham NHS Foundation
North Bristol NHS Trust
Cambridge University Hospitals NHS Foundation Trust
NHS Greater Glasgow and Clyde
Leeds Teaching Hospitals NHS Trust
St George's Hospital

Figure 3. UK HDClarity Sites Operating on Protocol Version 4

Further Information

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

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

Update: New Lesley Jones Seed Funds Awarded

Catherine Deeprose

The EHDN seed fund programme has been renamed in honour of Professor Lesley Jones, who was deeply involved in the review of applications. Funding has recently been awarded for two exciting new projects:

Franz Marxreiter

Franz Marxreiter at the University Hospital Erlangen, Germany, will work towards the more sensitive detection of motor symptoms in HD using sensors. Sensor data will be combined with video recordings of involuntary movements to develop algorithms to provide sensitive, objective and quantitative outcomes. It is hoped this approach will facilitate early motor diagnosis and more effective monitoring of disease progression.

Nicholas Allen

Nicholas Allen at Cardiff University, UK, will use stem cell models to address a novel hypothesis that mHTT protein transfer interacts with DNA repair modifier pathways and acts as a driver to increase CAG repeat expansion rates in receiving cells. This work aims to inform the understanding of the pathogenic burden of mHTT in HD.

The Lesley Jones Seed fund programme is intended to support pilot studies that will eventually kickstart larger projects. The next deadline for applications is 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.

Update: Funding Opportunities

Fionnuala Margreiter,
Grants & Collaborations Manager

EHDN/MDS-ES fellowship programme

We are delighted to announce that applications for the 2023 fellowships will be open soon. If you are a young clinician/health care professional from an area currently underserved in clinical services and would like to gain experience in a multi-disciplinary clinic in Europe, then this might be for you. Click here for more information: http://www.ehdn.org/hd-clinicians-researchers/fellowship-programme/

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

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**

Photos: Gabriele Stautner · artifox.com

Nora used music, photographs and videos to tell her story

Interview with Nora Guthrie: On Fuelling Hope

Nora Guthrie spoke as a special guest at the EHDN 2022 Plenary Meeting. As the daughter of the late American folk musician and singer-songwriter Woody Guthrie, who was diagnosed with HD in 1952 and his wife, Marjorie Guthrie, founder of the Huntington's Disease Society of America, Nora had a wealth of fascinating insights to share.

So, how you have found EHDN 2022?

It's been wild! I've not really been involved in the conference per se because I'm not a medical person or a researcher or anything like that. I just try to get the headlines at the end of the day.

There was quite a response from the audience at the end of your presentation! Were you surprised by this reaction?

Well, I think it was probably a nice break for everyone to have a little entertainment! My presentation had music, videos, storytelling and stuff like that. My husband always says it's a different way of looking at the same thing. You know, the scientists are looking at it from one perspective, and I look at it from another. People respond differently – some people respond to storytelling, others to music, and so on. So, I think having all of us together works well. We're all talking about helping people and how we help people. Some people use science to help people, and some use music, art or literature but we have this common meeting ground, and I think that's what we all respect and appreciate about each other.

Would you say your background has given you a unique perspective?

I was brought up in music and science and dance and illness and health and everything else, and it's been a wonderful experience. You can't limit a musician's brain to just music and you can't limit doctors to just charts. Everyone really does respond very similarly – to different degrees, but similarly. So that's what we try to do – bring everybody together.

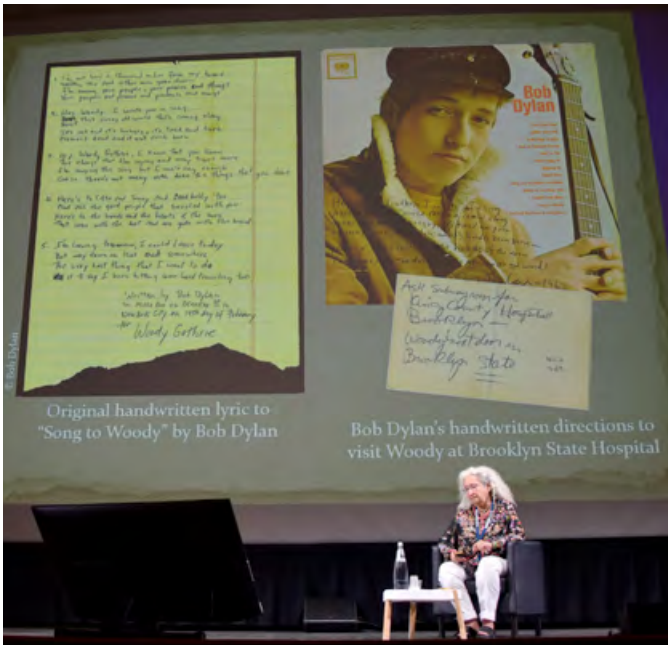
Which you seem to be able to do in an incredibly inspiring way…

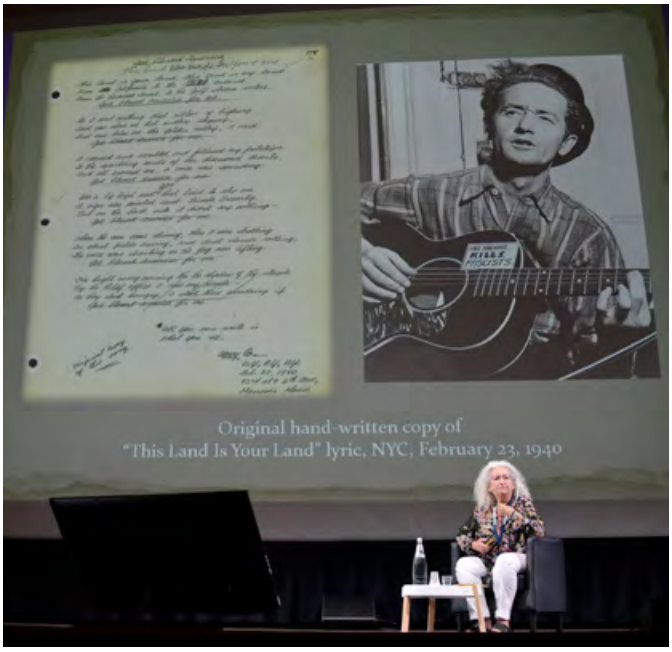
Well, I can't do it any other way, I don't really have a choice! It's who I am… all I can do is be myself and talk about what I know. Whenever someone invites me to speak at an HD conference or something like that, I don't try to be smart. I just try to be myself and people respond.

Could you talk a little bit more about the response you've got from the HD community?

Well, people came up to me and say, 'that was so inspiring'. But what do they mean? I don't really know but maybe they see in me something that they saw in my mother.

My mother put an ad in the New York Times, looking for one other person who knows somebody who had HD in 1967, and one person called. They sat together, drank





Photos: Gabriele Stautner · artifox.com

tea, and put out another ad. And then there were twelve people and suddenly there was an HD Committee! So, I think people see can see that every little activity can help – and that's inspiring. There's a place for everybody in the story and you can make a place for yourself, the way my mother did.

'Some people use science to help people, and some use music, art or literature but we have this common meeting ground…'

Sometimes, as just one person, you don't plan on making a difference, but somehow your destiny or just your will to contribute something ends up blossoming into a major change in society. Bob Dylan, who often visited my father in hospital, had this effect. He made a huge difference to society, although he didn't mean to. He had learned all my father's songs when he was a teenager (he called himself a Woody Guthrie jukebox) and my father would love to hear his own songs. And then look what happened… he sang a Woody Guthrie song or two, talked to all his friends about it, talked to Jimi Hendrix, talked to John Lennon, talked to all these other blossoming young musicians in the 60s and before you knew it, everybody in his generation had heard of Woody Guthrie.

My husband says the inspiration should be to keep doing what you're doing because you never know what's going to come out of it. That's also what happened with my mother when she was working in the early days visiting medical schools, talking to medical students, and saying 'you should go into hereditary research genetics'! No one was doing this in the 70s and early 80s and the whole new area of genetics was just a little sprig in the ground, just a little seed… but scientists like Michael Hayden and Jim Gusella came out of that period.

Now, when I go to HD meetings and see hundreds of people talking about HD, I look around and say to myself, 'every one of you, in some way, is here because of my mother'. They don't know it, and I don't have to talk about it. This year, in particular, there were so many young people, young researchers, and particularly young women, doing presentations and I thought, 'I hope my mother sees this. I hope she sees what she's done'.

For me, inspiration is a fuel. It's like going to the gas station and filling up – people get fuelled with something that makes them energised and want to keep going in their own way. If I can give fuel to people, I don't have to understand the science. That's not my job and I don't know anything about that. But I'll be the fuel that says, 'Go for it. Keep being you, keep studying, keep researching, keep doing what you're doing'.

Looking back, how do you feel the HD field has changed over the last 50 years or so?

When my mother started looking into HD, nobody wanted to mention that it was in their family and they

Photo: Gabriele Stauther · artfox.com

Nora carrying the CAG banner at the EHDN2022 in Bologna

might not have even known it was in their family. While there's still a stigma attached to having any hereditary disease, there's a greater sense of acceptance in the HD community. You're in a community where everyone has the same issues going on in their lives.

My father wrote this wonderful piece about hope – 'the note of hope is the only note that can keep us from falling to the bottom of the heap of evolution because all a human being is, anyway, is just a hoping machine'. We just keep hoping for the best and maybe that's part of the fuel that I try to give people. We are all in the same boat together called life. Next, it will be my daughter here carrying on this work, and then my granddaughter, and who knows who else. So, the legacy continues and I've come full circle too. I've come from feeling like I lost my parents, to being fuelled, and then coming back with the belief I have something to give now.

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Dates for your diary

- **#HuntintingtonsInMind: A free study afternoon on HD and mental health for professionals** will be delivered via Zoom by the Huntington's Disease Association on 9 November 2022. For further details and to register click here.
- **'All you need to know about PROOF-HD'**: The Huntington's Disease Alliance is presenting a webinar on the PROOF-HD study on 10 November 2022. Click here for registration and further information.
- The **HDYO Congress for young adults, families and professionals** impacted by HD will be held in person, 17–19 March 2023, in Glasgow, Scotland. The draft agenda is available here and for the latest updates visit https://hdyocongress.org/

Photo: wikipedia/commons

- **CHDI's next Annual Huntington's Disease Therapeutics Conference** will be held 24–27 April 2023 in Dubrovnik, Croatia.
- Registration will open soon for the **European Huntington Association conference** which will be held 19–22 October 2023, in Blankenberge, Belgium.

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