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EHDN *News*

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

Photo: G. Stautner for EHDN

Working groups and task forces: progress report

Michael Orth, Science Director, EHDN

Working groups (WGs) are a key pillar of EHDN's mission to improve the lives of people from HD families. Their activities feed into all three complementary strands of that mission: advancing research, conducting clinical trials and improving care. Though their overall goals have not changed over the years, the way they function within EHDN has. Since the inception of the think tank and, more recently, a sponsorship programme whereby Executive Committee (EC) members "adopt" WGs so as to be able to interact more closely with them, their goals and needs have become better understood within the organisation. This in turn has promoted closer connections between WGs working on related research topics.

Another realisation over time has been that important HD-related questions can sometimes be more swiftly and efficiently addressed by a focused task force (TF). TFs may also be sponsored by EC members, and in this issue of the newsletter we catch up with three of them – two that stand alone, on driving and dysphagia, and a third that has been set up by the Advanced Therapies WG.

Face-to-face meetings in the context of the biannual EHDN plenary meeting have always served to galvanise WG activity but that has not been possible this year, due to Covid-19. Videoconferencing can never entirely replace those meetings, but virtual meetings – for example, using EHDN's Zoom account – also have advantages. Interactions can be more frequent and planning more flexible. Such meetings cost less and, though they may not be as much fun, they spare participants the trials and tribulations of travel.

More information about the WGs and TFs can be found here.

Advanced Therapies WG

Romina Aron-Badin and William Gray, lead facilitators

This WG aims to maximise the rapid and effective translation of new treatments to patients, by identifying and strategically addressing current and future bottlenecks. We are focusing our efforts initially on the delivery of substances to the brain, the design of clinical trials, and how best to follow up and assess patients. These issues are addressed within the appropriate technical, regulatory and ethical frameworks, to provide realistic ways forward.

Given the breadth of issues to be covered, the WG has decided to constitute task forces to address specific challenges. The first was approved

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by the think tank in November 2020 and focuses on surgical delivery. It will deal initially with cell-based therapies, since this area is less well developed than genetic and small molecule therapies and presents its own challenges that will be relevant for combined therapies in future. In fact, many of the challenges raised by cell-based therapies are common to the direct delivery of all advanced therapies to the brain or cerebrospinal fluid (CSF). They include:

- **Target engagement:** are we delivering the right molecules/cells to the right places for their function to be optimal?
- **Distribution:** are we covering sufficient brain volumes and targets to have a positive impact on function?
- **Safety:** are we minimising potential surgical complications and optimising therapies during delivery?
- **Devices:** can we help design and develop better devices to deliver molecules/cells to optimise their survival and effectiveness once delivered?
- **Standardisation:** making procedures homogeneous across different centres to avoid variability in clinical trials

The TF's steering group has now been officially constituted by a core group of neurosurgeons and scientists from Cardiff University (UK), the Atomic Energy Commission (France), University of California, Irvine (UCI) Health (USA), and the University of Rochester (USA). The TF will dynamically co-opt expertise from industry, health and academic organisations and patient associations, working through organised meetings to target the challenges identified and produce recommendations by 2022.

Photos provided by R. Aron-Badin and W. Gray

Romina Aron-Badin and William Gray

Photo: Niels Skotte

Photo: G. Stautner, Artifox

Niels Skotte and Ed Wild

Biomarkers WG

Niels Skotte and Ed Wild, lead facilitators

The Biomarkers WG is a collaborative network of investigators addressing questions related to the discovery, understanding and clinical confirmation of biomarkers for HD. The WG places emphasis on biofluid resources and quality control, biomarker measurability, advantageous technologies, the use of preclinical data and the integration of -omics data.

Biosamples, including blood and CSF, along with extensive clinical datasets collected from international studies including Track-HD, TrackOn-HD and HDClarity, have formed the foundation of several projects designed to validate promising biofluid biomarkers and discover novel and complementary biomarker candidates for HD. Changes in the proteins neurofilament light chain (NfL), which is an axonal marker of neuronal injury, and YKL-40, an inflammatory mediator, are among the first to be detected in HD. The HD Young Adult Study (HD-YAS) recently found that these two proteins were elevated in CSF as early as two decades before onset, when no clinical, cognitive or psychiatric changes had yet been observed. Meanwhile, a two-year prospective longitudinal HD-CSF study published last June suggests that levels of NfL and mutant huntingtin protein (mHTT) may predict clinical disease status, disease progression and brain atrophy.

In addition to the ongoing characterisation of well-known HD biomarker candidates, extensive investigations have been conducted of biofluids using state-of-the-art proteomics technologies. New data highlight several interesting proteins in CSF that require further validation.

The ambition to generate defined patient biomarker profiles is within reach as a result of the ongoing development of assays, tools, and technologies that offer better precision, sensitivity and depth of molecular data, and thanks to the detailed clinical data provided by clinicians, researchers, HD gene expansion carriers (HDGECs), patients and families.

Please get in touch if you would like to join the group: niels.skotte@cpr.ku.dk, e.wild@ucl.ac.uk. We are particularly interested in those with expertise spanning preclinical and clinical research who can help us broaden our understanding of biomarker changes over time and after lowering of mHTT. Our next meeting will take place virtually on 21 May 2021, with updates being posted on our website.

Dysphagia TF

Christina Lang and Angela Nuzzi, lead facilitators

The dysphagia TF is a multidisciplinary panel of experts that aims to investigate the swallowing difficulties that occur in HD. It focuses on the assessment and management of dysphagia and its implications for, among other things, nutrition and pharmacological treatment. Christina Lang and Angela Nuzzi lead the TF, with the collaboration of Anne-Wil Heemskerk-van den Berg of Leiden University as a scientific expert on the topic.

Photos provided by C. Lang and A. Nuzzi

Christina Lang and Angela Nuzzi

Despite the importance of dysphagia in clinical practice, there is a paucity of literature on the problem. One of the aims of the TF is therefore to review existing clinical guidelines for the management of swallowing difficulties in light of studies that use instrumental swallowing evaluation in HD, and in light of experience with neurological conditions other than HD. The review will be conducted in 2021 with the collaboration of a panel of experts. Researchers working on this topic who would like to contribute are welcome to contact us: christina.lang@uni-ulm.de, angelanuzzi@hotmail.it

Following the update of the guidelines, the TF plans to identify and validate appropriate assessment tools and screening questionnaires that can be used over the course of HD, in order to provide information to the HD community and support collaboration between researchers and clinicians globally.

New driving simulator with moving base

Photos provided by Rients Huitema

Rients Huitema

Fitness to drive TF

Rients Huitema

The goal of this TF is to devise recommendations for assessing fitness to drive in HD. Such recommendations should be grounded in research but also general enough to be adaptable and useful for regulatory acceptance. The challenge is that legal frameworks differ considerably between countries even within the European Union, therefore the TF has begun by summarising national regulations with the help of experts in each country.

In the Netherlands, fitness to drive is assessed by the national driving licence authority through an on-road driving test. Although this kind of test is considered a gold standard in many countries, it may not detect some behavioural aspects of HD. For example, patients may compensate for specific deficits by adjusting their driving behaviour or planning their trip in advance. On the other hand, patients with impaired self-awareness may overestimate their driving skills. In a project initiated by

the University Medical Center Groningen, we will assess whether these behavioural changes can help predict fitness to drive in HD. The pandemic has put a temporary halt to the research, but since the Maastricht University Hospital has joined both the TF and the project, we hope to be able to double the recruitment rate as soon as the research gets started again.

An important instrument in all research on fitness to drive is a driving simulator. This allows us to study a subject's behaviour in a standardised way, but also in scenarios that could not be staged in the real world – for example, where other drivers do not abide by the rules of the road. Of course a driving simulator has shortcomings too. One is simulator sickness, which is caused by the mismatch between visual, vestibular and proprioceptive cues. In static driving simulators, for example, the subject does not feel accelerations and decelerations that result from braking or turning. Between 20 and 30% of subjects drop out of research due to simulator sickness. To minimise the problem we have equipped the simulator in one of our test sites with a moving base so that accelerations and decelerations are incorporated into the simulated driving experience.

Photos provided by N. Hobbs and R. Scahill

Nicola Hobbs and Rachael Scahill

Imaging WG

Nicola Hobbs and Rachael Scahill, lead facilitators

The Imaging WG is a collection of researchers from around the world who share ideas with the aim of developing best practice for the analysis of brain scans in HD. At the moment there is a real focus on using imaging for upcoming clinical trials. If we are to get meaningful imaging outcomes for these trials, there is a lot of work to be done to standardise both scan acquisition and analysis techniques.

We have been working with the Critical Path Institute, in collaboration with CHDI and a number of industrial partners, to compile two articles that we hope will inform the design of future clinical trials. The first is a review of structural volumetric MRI studies; the second, recommendations for the implementation of these biomarkers in clinical trials. We hope that both will be published this year. While structural MRI is a well-established technique, others are less well-known. These investigate properties of the brain such as connectivity of the white matter, brain activity, and measures of iron and myelin.

In the spring of 2021 we hope to convene an online meeting of the WG to discuss the latest ideas around these techniques so that we can start to reach a consensus on best practice. We hope to share data where possible, to maximise the benefit for the HD community.

At the moment we are quite a small group but we are keen to include new members who either bring specific imaging expertise, or who just want to learn about the best way to implement that expertise in a study. Please let us know if you are interested in joining us: r.scahill@ucl.ac.uk

Paediatric HD WG

Oliver Quarrell, lead facilitator, and WG members

As described in the November 2018 edition of the newsletter, a 2015 decision by the European Medicines Agency (EMA) meant that sponsors of novel treatments for HD would henceforth have to explain how those treatments would be assessed in children and adolescents with HD. Since the established term, juvenile or juvenile onset HD (JoHD), also includes young adults (whose disease onset occurred in childhood), in 2019 the WG published the definition of a new term, paediatric HD (PHD), which refers exclusively to under-18-year-olds affected by HD.

We have had a dialogue with the EMA advising them that there will be far fewer cases of PHD than of JoHD, in order to try to establish what is realistic in terms of the

availability of PHD patients for assessing new treatments. While not all PHD/JoHD patients have very large CAG repeat expansions – that is, more than 70-80 trinucleotides – the rare ones that do manifest with more severe disease, increased triplet mosaicism and an atypical phenotype compared to adults, along with reduced lifespan and specific neuropathological patterns (see this paper and its appendix for more information).

Photos provided by U. Jones, D. Kegelmeyer and A. Kloos

Una Jones ***Deb Kegelmeyer*** ***Anne Kloos***

Photo provided by Oliver Quarrell

Oliver Quarrell

We are working with the Huntington's Disease Youth Organisation (HDYO) to develop a register which *inter alia* will help families with PHD children to self-identify, because JoHD/PHD cases are heterogeneously distributed around the world. Due to variations in genetic background, they occur with a higher prevalence in certain regions, such as the Middle East, than others. In collaboration with HDYO and others, we are undertaking a systematic review of rating scales used in JoHD, the protocol of which can be found here.

Photo prov. by P. Nopoulos

Peg Nopoulos

We are also pleased to report that Peg Nopoulos of the University of Iowa has edited a special issue of *Brain Sciences* on JoHD, and that last October she and others also published a review of the neurodevelopmental hypothesis of HD. Although PHD/JoHD patients constitute a small population, our WG would like to acknowledge the support it has received to study these young people and their families. They will continue to require active support, research and care.

Physiotherapy WG

Una Jones, lead facilitator, with co-leads Deb Kegelmeyer and Anne Kloos

Over the 13 years of its existence, the Physiotherapy WG has developed two sets of clinical practice guidelines, and published a systematic review of physical therapy and exercise interventions for HD, along with several studies investigating the reliability and validity of outcome measures and the effectiveness of interventions. These papers are available at the WG's website.

The group has also produced physiotherapy resources for leading an active life, which are available on the European Huntington Association's website. An evaluation of that website indicated that the people using the resources included healthcare professionals, people with HD and family members, and that it had increased knowledge of ways of improving physical activity and the benefits that accrue from it.

In 2020 the WG focused on providing support for people with HD so that they remain active during the pandemic and associated lockdowns. Resources have been made available through the WG's website, as well as through patient associations in Europe, South America and the US.

In 2021, the group will support physiotherapists in the implementation of the most recent clinical practice guidelines for physiotherapy in HD, published in *Neurology* in 2020. These incorporate six action statements in relation to: aerobic and resistance exercise, gait training, balance exercises, breathing exercises, postural control interventions and end-stage care. We are carrying out a survey to explore the barriers and facilitators to implementation of these action statements, the findings of which will enable us to develop resources and strategies to support physiotherapists in their clinical practice.

At the WG's virtual meeting in January 2021, we decided to create four workstreams that will develop resources to support physiotherapists in implementing the 2020 guidelines in residential care facilities, specialist HD clinics and communities. The fourth workstream will be dedicated to physiotherapy students learning about the management of HD.

Physiotherapists who are interested in joining the group should contact Una Jones: jonesuf@cardiff.ac.uk

European Reference Network for Rare Neurological Diseases

Astri Arnesen, Alicia Brunelle, Caterina Mariotti, Marleen van Walsem and Ruth Veenhuizen

Photo provided by Holm Graeßner

Holm Graeßner of the University Hospital Tübingen, who coordinates the ERN-RND

The Covid-19 pandemic has taught us the importance of online tools. Through virtual platforms, information can travel from one part of Europe to the other in seconds. This can make a huge difference to people's lives, especially those living with rare neurological diseases. But what if healthcare professionals could also share their expertise virtually?

In 2017, the European Commission established the European Reference Network for Rare Neurological Diseases (ERN-RND), a virtual platform for treatment and diagnosis, and today, 41 specialist hospitals in 21 EU member states are collaborating via that platform to improve the diagnosis, treatment and care of people affected by rare neurological diseases.

In Europe, more than 500,000 people live with such diseases. Many have no local access to specialised treatment and an estimated 60% of them are undiagnosed. The ERN-RND covers six disease groups: Chorea and Huntington's disease; Frontotemporal Dementia; Atypical Parkinsonism; Dystonias, Neurodegeneration with Brain Iron Accumulation (NBIA) and Paroxysmal Disorders; Cerebellar Ataxias and Hereditary Spastic Paraplegias; and Leukodystrophies.

Mary Kearney represents the Cerebellar Ataxia and Hereditary Spastic Paraplegias category in the ERN-RND patient advocacy group. In an interview with the European Huntington Association last year, she said, "I'm coming from Ireland with a population of approximately five million people. There is no possible way we can have the expertise for every rare disease."

Photo provided by ERN-RND

ERN-RND coordination office and ePAG (European Patient Advocacy Group) representatives on Rare Disease Day, 29 February 2020, University Hospital Tübingen

Via a secure online platform called the Clinical Patient Management System (CPMS), multidisciplinary panels within the ERN-RND discuss cases. Moreover, ERN-RND working groups composed of clinicians and patients are developing clinical guidelines, diagnostic flowcharts and disease rating scales. The ERN-RND can therefore be seen as a hub that gathers medical knowledge in one (virtual) place. For it to be really effective however, collaboration with many organisations and patient representatives is essential.

Photo provided by Caterina Mariotti

Caterina Mariotti

"The added value of the ERN-RND is the possibility of having a structure that can provide practical help for guiding clinical and diagnostic procedures of several rare neurological diseases," says Caterina Mariotti, a neurologist at the IRCCS Carlo Besta Neurological Institute in Milan and a member of EHDN's Executive Committee. "In addition, several disease-specific networks, such as EHDN, are continuing their efforts to improve the treatment of people affected by rare neurological diseases. There is no competition between organisations promoting scientific research and care for such diseases. Synergistic strategies and communications should be envisaged."

Accessibility is key to improving the quality of treatment and care delivered to HD patients and their families. But, say Regina Marleen van Walsem and Ruth Veenhuizen, the lead facilitators of EHDN's Multidisciplinary Treatment and Care working group (WG), "Despite the many guidelines and best practice documents developed and made available in recent

decades, they are often available locally, regionally or in peer-reviewed scientific journals, and spread out over various online locations."

They see the ERN-RND as a good opportunity to amalgamate medical knowledge, and their WG has started collecting existing national and international guidelines in order to facilitate that goal. "We engaged in collaboration with the ERN-RND, which offers excellent possibilities to share knowledge, and to disseminate guidelines and best practice documents at one online location," say van Walsem and Veenhuizen.

They invite anyone who knows of a guideline that is relevant to the goal of the Multidisciplinary Treatment and Care WG to get in touch with them: r.m.van.walsem@medisin.uio.no, r.veenhuizen@amsterdamumc.nl

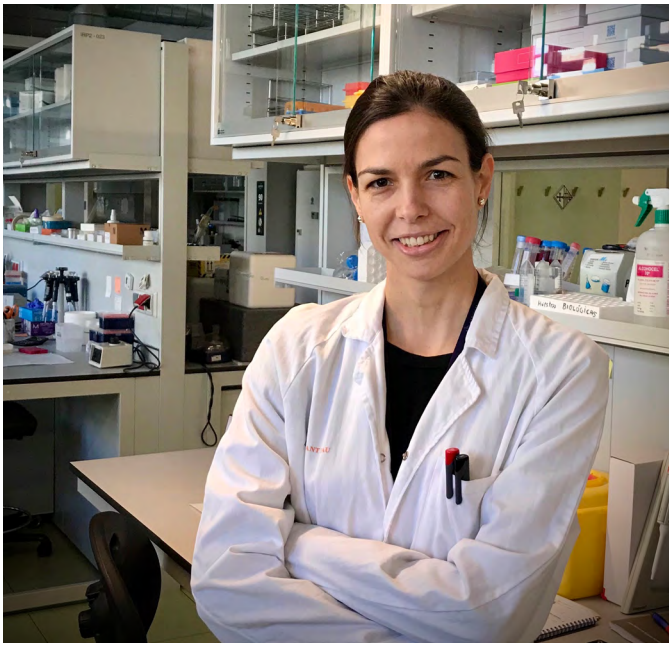

Photo kindly provided by Rocío Pérez González

Rocío Pérez González

New seed fund awarded

EHDN has approved seed funding for a project proposed by Rocío Pérez González of the Sant Pau Hospital in Barcelona, to investigate exosomes as potential markers of disease progression in HD.

Exosomes are small vesicles that are secreted by most cell types, including neurons, and that contain biological material reflecting the state of the cells that secreted them. For this reason they have been proposed as promising carriers of biomarkers in HD. Further investigation is needed, however, to identify disease-specific signatures in brain exosomes.

The Barcelona group will isolate exosomes from post-mortem HD and control brain samples and measure their protein composition in order to try to identify HD-specific signatures that correlate with brain pathology. Given that exosomes can cross the blood-brain barrier and reach the bloodstream, they could potentially serve as an accessible source of biomarkers for HD brain-related processes.

Seed funds are intended to support pilot studies that will eventually kickstart larger projects. The next deadline for applications is 1 November 2021. More information about the programme and how to apply can be found here.

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


Photo: G. Stautner, Artifox


Photo: Jenny Townhill

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 EHDN's Scientific and Bioethics Advisory Committee, which makes its recommendations to the Executive Committee. If endorsed, a formal letter 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.

DOMINO-HD

Recruitment for this EU-funded observational study, which is designed to provide new insights into whether behaviour and lifestyle factors are linked to HD genetic risk and progression, finally got underway in February following delays caused by the pandemic.

HD-DBS

This multicentre trial of pallidal deep brain stimulation for HD, sponsored by the University of Düsseldorf, is expected to finish recruiting this spring.

GENERATION HD1 and GEN-EXTEND

The Roche GENERATION-HD1 global phase 3 trial of tominersen (RG6042), an antisense oligonucleotide, completed enrollment in 2020, with 791 participants enrolled across approximately 100 sites in 18 countries. Study treatment and follow-up assessments are ongoing, and on completion, participants are offered the opportunity to enroll in the open-label extension (OLE) study, GEN-EXTEND.

PRECISION-HD1 and -HD2

WAVE Life Sciences expects to report data from both its ongoing PRECISION-HD phase 1b/2a trials, and available data from the related OLE studies this spring. The analysis will include biomarker and safety data from all dosing cohorts up to and including the 32mg cohort for PRECISION-HD2 and completed dosing cohorts for PRECISION-HD1 (including all participants from the 16mg cohort). These data are expected to support a decision regarding a potential phase 3 study. Participants from the phase 1b/2a trials have been enrolling into the OLE studies since 2020, and the vast majority of eligible patients have been enrolled. In December 2020, WAVE submitted a clinical trial application for WVE-003 (SNP3). This is WAVE's first HD candidate to use its novel PN backbone chemistry modifications which, according to preclinical data, increase the potency, exposure and durability of a compound. WVE-003 is also designed to selectively target the mutant huntingtin mRNA transcript while leaving the wild-type protein relatively intact. The protocol was also submitted to EHDN, which endorsed it in December 2020. WAVE expects to start dosing HD participants with SNP3 this year, once regulatory and ethical approvals are in place.

PROOF-HD

This Prilenia-sponsored phase 3 trial is evaluating the safety and efficacy of pridopidine in participants with early-stage HD. The study will enroll 480 participants aged 25 or older, with a clinical diagnosis of adult-onset HD, at approximately 60 clinical sites in the US, Canada and Europe. The first participant was recruited in October 2020. The treatment period will last for up to 18 months and there will be an optional OLE study. PROOF-HD is designed to replicate the previously claimed effect of pridopidine in maintaining functional capacity in patients with early HD.

SHIELD-HD

This two-year natural history study of HDGECs, sponsored by Triplet Therapeutics, is collecting longitudinal information related to somatic instability and DNA damage response genes, along with established assessments of disease progression. The study has enrolled 70 participants to date, and follow-up assessments are ongoing at sites in North America and Europe. The results will inform assessments ahead of a future treatment trial.


Photo: G. Stautner, Artifox

Update: Enroll-HD

Olivia Handley, Enroll-HD Global Platform Manager

Two exciting imaging studies funded by CHDI are set to launch in Europe in the next few months. The first, iMagemHTT, is a first-in-human adaptive positron emission tomography (PET) imaging study that will explore a potential mutant huntingtin radioligand for its binding and kinetic properties. Phase 1a will recruit healthy control participants, while subsequent phases will include healthy controls and HDGECs. The first participant was recruited on 9 February 2021, in Leuven, Belgium.

The second study, iMarkHD, is a longitudinal study looking at molecular pathology and neuronal networks in HDGECs and healthy controls, using PET and multimodal magnetic resonance imaging (MRI). The main cohort will be invited to attend study visits at baseline, one- and two-year follow-up. iMarkHD will be coordinated by King's College London, but due to the latest lockdown in the UK, it is not possible to accurately predict when the first participant will be recruited. It is hoped this will happen in March or April 2021.

Both studies have been able to leverage a range of support from the Enroll-HD platform, such as advice on site feasibility and selection. Early in the protocol development phase, study teams engaged with site intelligence leads Jenny Townhill and Tim McLean to explore which sites could be used as patient identification centres for iMarkHD, and which as clinical sites for iMagemHTT. It's worth noting that the platform, which has gained an invaluable amount of site intelligence over its decade-plus of existence, is now in a position to guide study teams as to which sites would be good candidates for inclusion in their studies. Its experience- and metric-based recommendations accelerate site selection significantly, by identifying not only those sites that are well placed to support recruitment, but also those that fit the study's needs in more specific ways, such as having research staff with experience in CSF collection and processing, or access to -80^{0}C freezers. This guidance is just the first step towards site selection, of course. It is combined with other information before the study team reaches out to a site to establish whether it is interested in taking part and has the resources to do so.

Particularly for iMagemHTT, the platform has been able to provide local support with ethics review board and institutional submissions too. The imaging centre for this study is in Leuven, and for practical and administrative reasons the study team has chosen to use Flemish-speaking clinical sites only to begin with, including sites in the Netherlands. French-speaking Belgian sites are aware of the study and are ready to lend support in screening French-speaking participants should the need arise. EHDN language area coordinators (LanCos) have helped enormously by smoothing communications and delivering high-quality translations quickly, thereby ensuring momentum has been maintained as the study has moved through the various approvals processes. The LanCos have experience of working with the site investigators and their institutions through Enroll-HD, they understand local study start-up requirements and have established good relationships with local patient associations. They are therefore proving invaluable to study teams as those teams undertake complex start-up activities, often across multiple countries and sites.

As more and more clinical studies and trials seek access to the Enroll-HD platform, it is hoped that each new experience will help the platform grow and become better equipped to support the HD research community.

EHDN pays tribute to two giants of the HD community

Covid-19 robbed us of two colossi of the HD community this year, without whom scientific understanding of the disease – and in particular genetic counselling – would not be as sophisticated as it is today. Coincidentally, Marina Frontali and Peter Harper are linked by more than their burning curiosity about genetic disease and its implications; Marina went to Wales to learn from Peter, early in her career, and subsequently brought his ideas back to Italy. Here friends and members of EHDN pay tribute to them.

Photos kindly provided by A. R. Bentivoglio

Marina Frontali
(1941-2021)

Anna Rita Bentivoglio

I met Marina Frontali in the distant 1980s, when the Italian National Research Council (CNR)'s Institute of Translational Pharmacology in Rome, where she worked as a medical geneticist, and the Institute for Neurology at the Catholic University of the Sacred Heath (also in Rome), where I was working as a neurologist, launched a collaboration. This led to the opening of a monthly outpatient clinic dedicated to HD patients and families. With Marina's alter ego, the young psychologist Gioia Jacopini, we took a pioneering multidisciplinary approach, bringing relief to patients in a problem-centred fashion.

Marina's professional life had already taken a dramatic turn by then. Having trained in psychology, around the end of the '70s – with the support of her husband, the population geneticist Luciano Terrenato – she decided to attend a genetic clinic. It was here that she realised the need for a synergistic approach, combining psychology and genetics to support people with genetic diseases. Peter Harper's work on the genetic counselling of individuals at risk of HD had begun to appear in the literature. Marina moved to Cardiff to work with Peter and later returned to Rome with the intention of applying his approach in the Lazio region.

It is difficult to imagine how hard it must have been to establish a body of epidemiological research on HD, a disease that was barely diagnosed in Italy at that time.

Photo kindly provided by G. Evers-Kiebooms

Marina and Gerry Evers-Kiebooms in 2008.

Photos: G. Stautner for EHDN

Marina at the EHDN plenary meetings in 2010, and 2014 with B. Landwehrmeyer

She had to comb the archives of Roman hospitals to find the records of patients diagnosed with HD, track down their relatives scattered across the region, and then try to contact them to arrange genetic counselling and blood tests. The research was not funded, but Marina's enthusiasm was contagious and led to precious collaborations – with Gioia, with the social worker Carolina Casciania, and with some brave and generous geneticists. Marina described the experience of meeting HD families, often in remote villages, as "intensely enriching".

In 1982, by which time presymptomatic and prenatal testing based on linkage had become available for HD, Marina became a geneticist and moved to the CNR's Institute of Experimental Medicine, later the Institute of Neurobiology and Molecular Medicine, where she served as associate director until her retirement. She became a reference in her field, leading international projects with Jim Gusella and Peter Harper on HD gene mapping and the ethical and social aspects of genetic testing for late-onset diseases, respectively.

She continued to offer genetic counselling at the headquarters of the Italian HD association, AICH Rome, and she developed a model of counselling that embraced the psychological and ethical implications of testing for hereditary conditions in non-symptomatic, at-risk individuals. As a member of the CNR's bioethics committee, with Stefano Rodotà, an authority in privacy law, she drafted guidelines on the use of genetic data.

Marina and I were co-principal investigators at the Registry study site in Rome from 2004 to 2011. She was an active member of EHDN from the beginning, and from 2007 she served as co-lead of the Genetic Testing and Counselling working group, which produced the current guidelines on predictive testing. She was a member of the Enroll-HD ethics working group in 2011, and of EHDN's Scientific and Bioethics Advisory Committee (SBAC) for five years from 2014. As Kathrin Reetz, Chair of the SBAC told me, that committee benefited greatly from her expertise in neurogenetics.

Marina's sense of humour and ability to face life with a light heart went hand-in-hand with great seriousness and conscientiousness. And she was so tough! The only time I knew her to be late – by 30 minutes, for a lecture – I found out later that it was because she had had surgery for a cataract that morning, and couldn't immediately drive.

Last November her husband Luciano contracted Covid-19, which swept him away in a few weeks. Refusing to let him finish his days in hospital, Marina brought him home, where he died on 4 December, his hand in hers. Twelve days later she was hospitalised with Covid-19 in her turn, and she died aged 79 on 12 January. The doctor who telephoned her sister Francesca with the news was crying, and it took all of us who knew her by surprise. But Marina disliked pathos, and so we will remember her for her cheerful smile and her fierce intellect, which remained sharp until the end.

Photos kindly provided by Anna Rita Bentivoglio

Marina Frontali (right) with Gioia Jacopini

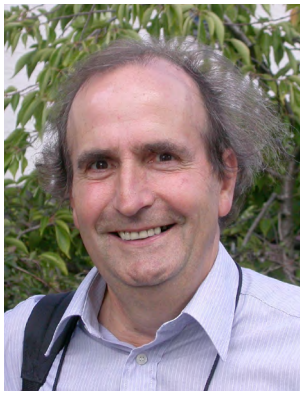

Photo kindly provided by Julian Sampson

Peter Harper
(1939-2021)

Lesley Jones and
Oliver Quarrell

We are greatly saddened to learn that Peter Harper passed away on 23 January, having suffered a stroke and subsequently contracted Covid-19. He will be greatly missed.

Peter was unusual in being a general physician, a medical geneticist, and an outstanding academic, teacher and mentor. He was a colossus in human genetics, recognised nationally and internationally for the breadth of his work in the field. Notably, he was instrumental in the discovery of the genes for HD and myotonic dystrophy, two landmark achievements.

When Peter came to Cardiff in the 1970s, there were a considerable number of referrals from HD families requesting genetic counselling. He established a service for the patients, employing people to visit them at home as well as providing hospital-based support. He undertook a detailed prevalence study of HD in South Wales, and developed a life-table approach to derive age-based risk estimates which is still in use today. In those days, the main international HD meeting, which Peter attended regularly, was small. He advocated greater integration with the patient organisation – something we take for granted today.

At that time, gene mapping was in its infancy. Peter developed a research group to undertake linkage studies for a range of genetic conditions. He set up the Institute of Medical Genetics in Cardiff, an unusual joint enterprise between the National Health Service and a university. When the HD gene was localised to chromosome 4 he confirmed that this was also the case in families from the UK. His research group was part of the international collaboration which resulted in the cloning of the HD gene, and he was instrumental in the development of our current predictive testing guidelines.

Photo kindly provided by Julian Sampson

Peter Harper in his office in Cardiff in the 1970s

Peter was unusually prescient about the familial and societal implications of predictive medicine, and he used his foresight to influence government policy. He was part of the UK advisory group that developed a moratorium on the use of predictive genetic tests in life insurance. His ability to think through the consequences of increasing access to genetic information led him to establish the UK Huntington's Prediction Consortium, partly as a forum in which to discuss difficult cases, and the UK Huntington's Disease Network. Both still exist, the latter as part of EHDN.

Photo: G. Stautner for EHDN

At EHDN2018 plenary meeting in Vienna

Peter was a prolific writer and his seminal book on HD, first published in 1991, is now in its fourth edition and edited by others. He edited an equally authoritative book on myotonic dystrophy. His influential textbook, *Practical Genetic Counselling*, arose partly from his work in HD and myotonic dystrophy. As a mentor he was hugely generous in developing many people's careers. A generation of scientists, medical and non-medical, is indebted to his encouragement. After he retired from clinical medicine, he took up a new career in documenting the history of discoveries in medical genetics, interviewing many of the founders of the field and generating fascinating oral and written histories.

Despite his many achievements and honours, which were honoured with a knighthood in 2004, he was always modest and mild-mannered. In time his wife Elaine, children and grandchildren will be glad to know that his many friends and colleagues in the global HD community were thinking of them at this time, and of the huge contribution that he made to the fields of HD and medical genetics.

Send us your photos!

In a visual monument to the Covid-19 pandemic, the Belgian Enroll-HD group poses in front of the double helix staircase at the Institute of Pathology and Genetics (IPG) in Charleroi, Belgium.

The photo was taken by Christelle Guichard on 2 November 2020 and shows, from left to right, **Cécile Minet, Dominique Van Paemel, Christine Verellen-Dumoulin and Michel Dupuis**.

Since May 2020, Christine Verellen-Dumoulin tells us, all patients and their families visiting the IPG have been required to wear a mask, as have all members of the Enroll-HD team – but the work goes on.

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

News from HDYO

EHDN extends heartfelt congratulations to the UK's Matt Ellison, founder of the Huntington's Disease Youth Organisation (HDYO), who was awarded an MBE (Member of the Most Excellent Order of the British Empire) in the Queen's New Year Honours List 2021, "for an outstanding achievement or service to the community which has had a long-term, significant impact". Matt, whose father had HD and who has tested positive for the HD mutation himself, founded HDYO in 2012 to support and educate young people from HD families. Since then, around 6,000 young people and their relatives have contacted HDYO, from more than 90 countries (HDYO will organise its international congress online this year, on 13-14 March).

HDYO is asking young people affected by HD to take part in an online survey on their experiences of lockdown during this pandemic, and how the organisation may be able to support them going forward. The survey can be found here and any questions should be addressed to Matt: matt@hdyo.org.

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Enroll-HD announces PDS5

The eagerly awaited fifth release of the Enroll-HD periodic dataset, PDS5, is now available for download. PDS5 contains rich longitudinal data from 21,116 Enroll-HD study participants. Data from 71,682 study visits are included, making it one of the largest cohort datasets that is openly available to researchers. An overview of PDS5 can be found here. As with all previous Enroll-HD datasets, it can be downloaded by any verified researcher through a straightforward, secure process. Please visit the Enroll-HD data access page for more information.

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Dancing at the Vatican

The wonderful 38-minute documentary *Dancing at the Vatican* is now free to view on YouTube in six languages – English, Spanish, Italian, French, Portuguese and German. As regular readers of this newsletter will know, the film follows the journey of some incredibly brave families from their homes in Latin America to the Vatican in Rome. All the families are bound by the same devastating disease, HD, and their life-changing mission to bring this long stigmatised disease out of the shadows culminates in Pope Francis becoming the first global leader to recognise HD publicly and to speak its name out loud.

If you enjoy the film please help spread the word on social media, using Twitter tag @dancing_vatican and Facebook tag @dancingatthevatican.

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Advertising two HDSA fellowships...

The Huntington's Disease Society of America (HDSA), with the generous support of the Berman and Topper families, is offering a "**HD career development fellowship**" to investigators with a doctoral or medical degree who are within five years of obtaining their PhD or completing residency/fellowship. The deadline for applications for the three-year grant of up to US$80,000 a year is 19 March 2021. Notification of an award will

be by late May for a fellowship to begin no later than 1 August 2021. More information can be found here.

The HDSA is also accepting applications for the **2021 Donald A. King Summer Research Fellowship**, which provides funding for undergraduate life science, pre-medical and first-year medical students to complete a summer research project under the direction of an established HD researcher at an accredited institution in the US. The deadline is soon, 5 March 2021, with notification by mid-April and a fellowship start date of the beginning of summer 2021. More information about this award can be found here.

...and two prizes

Nominations are open for the **ALBA-FKNE Diversity Prize 2021**, which aims to highlight a scientist or group that has made outstanding contributions to promoting equality and diversity in brain sciences, but the deadline is soon – 8 March 2021! More information can be found here.

Nominations are also open for the **Eric Kandel Young Neuroscientists Prize 2021**, which is awarded by the Hertie Foundation and the Federation of European Neuroscience Societies (FENS) and recognises outstanding work by early career researchers in any field of neuroscience. For more information, please visit this website. Deadline for nominations: 1 May 2021.

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Photos kindly provided by Clifford Stott

A steep learning curve:

Interview with Clifford Stott

Social psychologist Clifford Stott of Keele University in the UK is a member of the Scientific Pandemic Influenza Group on Behaviours (SPI-B) that is advising the UK government on how to manage the Covid-19 pandemic. He instigated and co-chairs SPI-B's security and policing subgroup. In his career to date, which he discussed in a recent BBC radio interview, he has been influential in changing the way police manage crowds – notably football crowds – so that disorder becomes less likely. His family is affected by HD and here he talks frankly about the difficulty of living with the disease, inside pandemics and out.

Can you tell us about your HD connection?

My ex-wife Michelle has HD and our two grown-up children are at risk of it, though they haven't been tested. Michelle inherited the mutation from her mother, though in that family Michelle was the first to acknowledge the disease openly, and we had our first child without knowing it was in the family. When our second was conceived we suspected the mutation was present. Michelle is now symptomatic and in a care home.

I'm sorry to hear that. Has the fact that you are a psychologist shaped your attitude to the disease?

Absolutely, it has shaped the way I've coped with it. You don't interact with HD without understanding its implications, and very early on I understood that the disease affects you in three ways: biologically, psychologically and socially. My position has always been that there's nothing you can do about the biological, yet, but you can manage the psychological and the social – not just with regard to the gene carrier herself, but also to the people around her.

To begin with, did you get the care and support you needed as a family?

Not really. We found out that Michelle had HD only about a decade after predictive testing became available. The concept of "presymptomatic" was relatively new and the support networks for people in that phase weren't really in place. Also, we were in our 30s and we wanted to live our lives, but when we did attend meetings the other people there were mainly elderly and symptomatic. We couldn't really relate to them, and we didn't want to have to confront what lay ahead before we had to. Where we live, in Merseyside, northwest England, we couldn't find medical expertise in HD. The only way we could access it was to take part in HD-related research at the University of Manchester. It was while participating in that research, that Michelle was diagnosed as symptomatic.

Did the situation improve?

Not really. I've had to engineer a really complex solution to protect my family's psychological, emotional, financial and physical wellbeing. First I divorced my wife and she became legally independent of me. At the same time the children and I established power of attorney over her [power of attorney refers to the legal authority to act for another person]. Once Michelle was divorced the welfare system became responsible for her care, but because we also continued to care for her, and because she continued to live in the family home, that posed an issue for the authorities. So while coping emotionally with her decline we also had to struggle to get her both the care and the benefits she was entitled to. In the end Michelle deteriorated so much that it was no longer safe to keep her with us, and she moved into a home. That was in late 2019.

A few months later England entered its first lockdown, to try to contain the spread of Covid-19. How did that affect your family?

Michelle was still getting settled into the home when the lockdown came into effect, and apart from a couple of visits last summer we didn't see her from March to December 2020. We managed to set up Facebook Portal in her room – a videoconferencing tool that looks like a picture frame, with a simple user interface. That worked for a while, but in August she stopped answering our calls. Luckily we were able to spend time with her at Christmas, with the support of the care home which allowed her to leave.

How do you explain your negative experiences of the health and social care systems?

I think it comes down to the failure of the UK government to take mental health seriously, combined with the effects of austerity on those systems. Also, in everyday situations HD is not a disease that is understood or that inspires solidarity in the way that, say, cancer does. I saw that firsthand, because Michelle was diagnosed with breast cancer three weeks after being diagnosed with HD. The contrast could not have been starker. Suddenly, care, support and understanding were available to her – for her cancer – that simply had not been for her HD.

It's been a rollercoaster of a year for you. Has being a member of SPI-B taught you anything?

I've learnt a tremendous amount, especially about the interface between knowledge and practice. I think academia has a huge problem in how it thinks about and communicates expertise. It's something I've given a lot of thought to, because I have had to engage with stakeholders – the police, in my case – in a highly politicised area, which is public disorder. The police don't want theory, they want solutions, and that's what I've always tried to give them. I took the same pragmatic attitude into SPI-B too, but I think as a whole that group places too much emphasis on

Source: CNN

Clifford Stott being interviewed by Christiane Amanpour for CNN during the pandemic

epistemological certainty. Sometimes, if you focus too much on that, then by the time your paper lands on the minister's desk it's too late – the decision has been taken. The emphasis needs to be on rapidity, on anti-Scipating the next policy decision and pulling together the best possible analysis quickly, so that the minister is armed with the arguments she needs to sway that decision.

Clifford Stott and family

Does your family situation ever influence your deliberations in SPI-B?

Occasionally, yes. Take the issue of vaccine certification, for example. There are essentially two ways you can approach this. You can say to people, unless you have been vaccinated and have a certificate to prove it, you can't do this or that. Or you can say, once you've been vaccinated and you have the certificate, all these things become possible that weren't before. Colleagues and I have shown that people are much more likely to accept the latter, enabling form of certification. And because they consider it more legitimate, it's more likely to have the desired effect. It would also make my life easier. Believe me, I would be very happy if I had a certificate that enabled me to go and visit Michelle in her care home.

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Dates for your diary

Save the dates for:

- HDYO's International Young Adult Congress 2021 (virtual), 13–14 March 2021
- 16th Annual HD Therapeutics Conference (virtual), 27–29 April 2021
- May is Huntington's Disease Awareness month. It will look a bit different this year, due to Covid-19, but there are still ways to get involved…

- EHDN2021 remote meeting (virtual), 09–11 September 2021
- FENS Brain Conference: "RNA mechanisms and brain disease", Rungstedgaard, Denmark, 20–23 October 2021