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EHDN News

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

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Outgoing, incoming and past (and founding) EHDN Chairs: Jean-Marc Burgunder (L), Anne Rosser, Bernhard Landwehrmeyer.

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EHDN2018: From little acorns grow mighty oaks

Laura Spinney

The 10th plenary meeting of the European Huntington's Disease Network and the 17th meeting of the European Huntington's Disease Association (EHA) took place in Austria's capital and "city of music", Vienna, from 14-16 September 2018. The combined conference happened to coincide with events related to Austria's Presidency of the Council of the European Union – which it assumed two months earlier – and although heightened security around those events temporarily impeded delegates' access to the conference venue, the Austria Center, it didn't dampen their enthusiasm. EHDN2018 was attended by 1,033 people from 47 countries – the highest and most internationally diverse turnout of any plenary meeting since the EHDN was born in 2004.

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If the spirit of the 2014 meeting, which marked the network's 10th birthday, was one of cautious optimism, the spirit of this one was tempered excitement. The HD research landscape has shifted significantly in the last four years, with one huntingtin-lowering therapy now in clinical trials, a second set to enter that phase soon, and further trials on the horizon. Although a hopeful view would be that these therapies could be available within 10 years if all goes well, the HD community is also aware that a disease-modifying treatment could take a lot longer to reach the clinic.

A full report of the plenary meeting is in preparation, and this newsletter is designed to draw your attention to some of its highlights. It's no coincidence that the largest section is devoted to clinical trials, but many other subjects were discussed too, and delegates won't easily forget the three brave individuals – Mathias and Birgitta Falk, and Victoria Emerson – who so movingly described their direct or indirect experiences of HD. EHA President Astri Arnesen, who talked about her own family's struggle with the disease, reminded us that while managing patients' expectations will be important as these clinical trials go forward, hope is what keeps HD families going. Three excellent documentary films – *Absolute Beginners, Dancing at the Vatican* and *The Unwanted Inheritance* – hammered that message home.

The meeting also provided an opportunity to pay tribute to outgoing executive committee (EC) Chair Jean-Marc Burgunder, who in the last four years has overseen the smooth transition of the EHDN from a more operational to a more strategic role, with the major observational study Enroll-HD, the working groups and the HD Science Think Tank at the heart of all it does.

Clinical trials – past, present, future

There is no doubt that the session that generated the most excitement at EHDN2018 was the final one, in which **Sarah Tabrizi** (London) summarised the results of the phase 1/2a trial of an antisense oligonucleotide (ASO) completed in 2017 by Ionis Pharmaceuticals, and **Scott Schobel** (Basel) described how his company, Roche, plans to build on those results.

The Ionis trial showed that the ASO produced a dose-dependent reduction of mutant huntingtin (mHTT) protein in subjects' cerebrospinal fluid (CSF) of up to 60% at the highest doses. Though it wasn't designed to detect clinical improvement, some intriguing, unidirectional effects on patients' Unified Huntington's Disease Rating Scale (UHDRS) scores were reported too. Ionis has now licensed the drug to Roche, which has renamed it RG6042. A 15-month open-label extension to the initial trial has been fully recruited at nine sites, while a 15-month natural history study will start imminently at 17 sites with 100 early-stage patients. Roche also plans a pivotal phase 3 trial, to test the drug's efficacy and safety in 660 manifest patients over 25 months. This will open early in 2019, with recruitment getting underway soon after that. Though the hopes of many HD families are riding on that trial, **Ed Wild** (London) warned that the very earliest any effective treatment resulting from it is likely to reach the clinic is about five years from now.

Another promising huntingtin-lowering approach in clinical trials is that of Wave Life Sciences, as described by **Michael Panzara** (Cambridge, Massachusetts). Wave exploits the fact that certain molecules exist in different orientations that aren't superimposable, and that the mirror-image or "stereopure" forms of such molecules may have different mechanisms of action and hence therapeutic effects. They have manipulated that chirality to develop stereopure ASOs that selectively target the mutant allele of the *HTT* gene, because they bind to tiny genetic variations called SNPs that "ride along" with it. About two-thirds of HD mutation carriers also carry one of two such SNPs that Wave has identified, or both, and two ASOs – one targeting each SNP – are being tested in parallel phase 1b/2a clinical trials. The topline results for these two trials, called PRECISION HD1 and PRECISION HD2, are expected in the first half of 2019.

Taking an entirely different approach to disease modification, Fanny Mochel (Paris) is coordinating two clinical trials – one of a molecule found in grape skins, resveratrol, and the other of a synthetic oil called triheptanoïne – to try to confirm preclinical findings that these compounds improve the brain's energy metabolism,

potentially protecting it from HD. Meanwhile **Monica Busse** (Cardiff) and her colleagues are running a clinical trial of a 12-month, structured exercise programme to try to get a clearer picture of whether exercise can interfere with the HD disease trajectory. PACE-HD, as the trial is called, has recruited 51 of a projected 120 patients to date.

Ralf Reilmann (Münster) presented two recently completed trials, Pfizer's Amaryllis and Teva's LEGATO-HD. Amaryllis tested a PDE10A inhibitor that, it was hoped, would alleviate the motor symptoms of HD by improving connectivity between the brain's striatum and cortex – the striatum being a region deep in the brain that is affected early in HD. LEGATO-HD was a huge global study of an immune system modulator called laquinimod. Both trials failed to meet their primary endpoint – improved motor function as measured by the UHDRS-total motor score – but in Amaryllis improvements in motor coordination were detected on the more objective Q-Motor test, while LEGATO-HD met a secondary endpoint, which was that the drug slowed the shrinkage of a striatal structure called the caudate nucleus. Reilmann said analysis of the LEGATO-HD data concerning secondary and exploratory endpoints continues, and researchers are discussing whether the Q-Motor changes seen in

Amaryllis are worth pursuing. In another recently completed clinical trial called HD Brain-Train, **Marina Papoutsi** (London) and colleagues replicated the findings of an earlier pilot study, that a non-pharmacological intervention called neurofeedback, targeting activity in the brain's supplementary motor area, slows HD progression – at least temporarily.

Other clinical trials are in the pipeline, including trials of novel huntingtin-lowering therapies. At uniQure, for example, **Pavlina Konstantinova** (Amsterdam) is working on a form of RNA

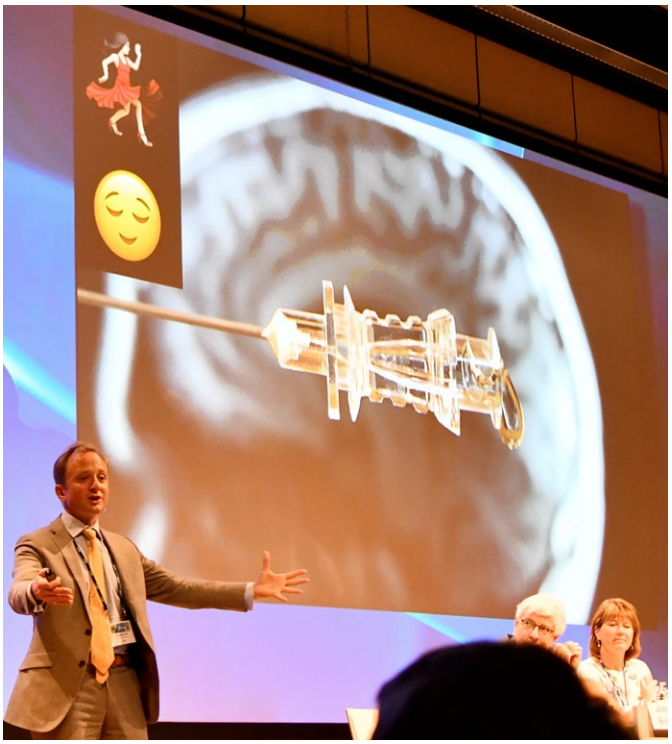
interference that involves microRNA. Her group uses an adeno-associated virus called AMT-130 to deliver an artificial microRNA that blocks the *HTT* gene, knocking down both mutant and wild type forms of the protein it encodes. In a rat model of HD, a single intracranial injection of AMT-130 resulted in a dose-dependent reduction of mHTT in both the cortex and striatum, improved motor coordination and longer survival. uniQure plans a clinical trial of AMT-130 in 2019.

At PTC Therapeutics, meanwhile, **Anuradha Bhattacharyya** (South Plainfield) and her team have identified small molecules that enter the nucleus of cells carrying the HD mutation, and modulate the splicing of HTT precursor mRNA (pre-mRNA) such that an exon with a premature stop codon is introduced. This acts as a signal that the mRNA should be degraded rather than translated into HTT protein. The PTC team has shown that this approach lowers HTT in HD patient-derived skin cells and neurons, and reports a roughly 50% reduction of HTT in CSF in two fully humanised mouse models of HD following 21 days of oral administration of the molecule. Bhattacharyya estimates that PTC will launch its first human trial of the approach in 2020. If it works, it will be a major advance since the therapy could be delivered orally, as a pill.

Huntingtin-lowering strategies that are further from clinical trials, but nevertheless show promise, include an SNP-guided CRISPR/Cas9 gene editing system that **Beverly Davidson's** group (Philadelphia) is working on, that selectively knocks down mHTT, and a self-inactivating variant of CRISPR/Cas9 invented by **Nicole Déglon** (Lausanne) and her team, called KamiCas9.

Tracking change

In order to measure how an experimental therapy affects the disease process in humans, you have to have biomarkers that reliably reflect that process. The development of sensitive and specific biomarkers for HD is therefore almost as important as the development of the therapies themselves.



Ed Wild said that major advances had been made in the biomarker field in recent years, and assays now exist for detecting and measuring mHTT in CSF, and neurofilament light (NfL) protein – another potentially powerful marker of HD onset and progression – in CSF and blood. Recent work by Wild's colleague Lauren Byrne (London), who herself comes from an HD family, has helped tease out which aspects of the disease each marker is most sensitive to, at which stage.

In a project funded by an EHDN seed grant, **Rosanna Parlato** (Ulm) has been investigating whether changes in the nucleolus – an organelle found inside the cell nucleus – are predictive of disease progression. Ribosomal RNA (rRNA) is made in the nucleolus, but its synthesis is altered when the cell is under stress or mutant RNAs and proteins are nearby, and mHTT inclusions are often found close to nucleoli in HD. Having analysed nucleoli in different tissues, in HD mouse models and in patients, Parlato found that nucleolar function was affected differently in the striatum and in other tissues such as skeletal muscle. The stage of the disease had an impact on it too, suggesting that this line of research might be worth pursuing.

Svetlana Kopishinskaya (Nizhny Novgorod) thinks that retinal thickness – as measured by a non-invasive imaging technique called optical coherence tomography (OCT) – could provide a reliable biomarker of HD, because retinal neurons start to degenerate early in the disease. Based on studies in HD patients, she reported that the pattern of change in the eye she and her colleagues have observed over the course of the disease appears to be specific to HD. Various measures of retinal thickness show a correlation with clinical scores of disease progression, and two in particular – relating to the retinal ganglion cells complex and the peripapillary retinal nerve fibre layer – are particularly sensitive to change in the premanifest phase. They could therefore be harnessed for early diagnosis and monitoring of disease progression.

The HD Clinical Trial Site Certification initiative offers a unique opportunity for sites with the capability to participate in HD trials to register their interest in doing so. While certification does not guarantee selection, it raises a site's profile with sponsors and increases the likelihood that it will be considered. The majority of Enroll-HD and many non-Enroll-HD sites have been certified, and we encourage sites that have not yet applied to do so. For more information please write to: hdsite@euro-hd.net

The earlier the better

One recurring theme of the conference, that emerged in sessions dealing with different aspects of HD, was the recent refocusing of attention on the premanifest phase.

For example, **Alexandra Durr** (Paris) pointed to one of the most interesting findings of the TRACK-HD observational study, which was that despite the loss of whole-brain volume over 36 months in that phase, cognitive and motor function did not deteriorate significantly over the same period. This indicates that the brain's attempts to compensate for the damage caused by HD are effective for a while, and could potentially be enhanced to delay disease onset.

Summarising years of research on environmental enrichment (EE) as a potential therapeutic avenue in HD, **Stephan von Hörsten** (Erlangen) said that although EE is controversial – mainly due to a lack of methodological standardisation making it hard to replicate findings – there is no doubt that it keeps brain cells functioning and slows disease progression, and that in mice, the effects are most potent in juveniles. "The earlier the better," he said.

People affected by juvenile HD have, by definition, a shorter premanifest phase than those with the adult form

of the disease, but as **Oliver Quarrell** (Sheffield) told the conference, a 2015 decision by the European Medicines Agency (EMA) – to drop HD from the list of diseases that benefit from a class waiver – is forcing the HD community to redefine this population. A class waiver allows trial sponsors to enter a simplified regulatory process to get a drug licensed, because they are not required to study its effects in children. This may be because the drug is unsafe in children, for example, or because the disease only affects adults. The grounds the EMA gave for its decision were that juvenile HD accounts for 6% of all HD, meaning that the disease does affect the paediatric population, which also has therapeutic needs. In the HD community, however, the term juvenile HD is used as shorthand for juvenile *onset* HD, which is defined as HD with an age at onset of 20 or younger. In reality, therefore, the majority of juvenile HD patients are adults. The EHDN charged the juvenile HD working group with rethinking these labels, and the working group is now proposing to replace them with the term paediatric HD

(PHD), where PHD refers to those 18 years of age or under who are currently affected by the disease.

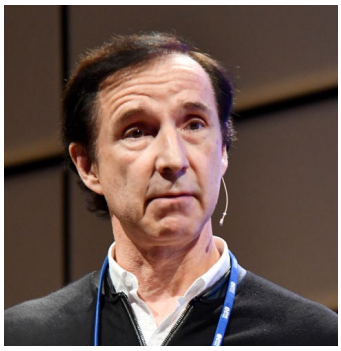
Cat Martin (Glasgow) said that young people in the presymptomatic phase of HD were going to play a critical role in future clinical trials, but that they are still relatively neglected as a population and therefore not sufficiently engaged in HD research. A survey of the opinions of young people from HD families on the information and support available to them was published in 2016 under the eloquent title, "Important but not enough". The EHDN's young adults working group, of which Martin is co-lead facilitator, is now working to get them more involved in HD research by making sure that they are better informed about upcoming trials and studies.

The devil's in the detail

The size of the CAG expansion determines the age at onset of HD, but it isn't alone. Since the Genetic Modifiers of Huntington's Disease (GeM-HD) consortium published its 2015 genome-wide association study (GWAS), showing that many genes influence onset, researchers have been busy disentangling the myriad interactions and modifications that shape the disease process, determining both onset and progression of symptoms.

Lesley Jones (Cardiff) of the GeM-HD consortium gave the example of *FAN1*, a gene involved in DNA repair that has a powerful effect on age at onset. In new work, her group has sequenced the protein-coding regions of the genomes of 500 patients whose disease onset was much earlier or later than predicted by their CAG repeat length alone, and shown that variants of *FAN1* affecting its DNA binding and nuclease activities are likely to be associated with earlier onset. DNA repair pathways aren't yet well understood, in the context of HD, but recent research has shown that they affect somatic instability – that is, variability in the length of the CAG expansion in different cell types in the same body – potentially affecting age at onset that way. The Cardiff group also found, to their surprise, that some of those who had

experienced early onset had pure CAG repeats in the expanded tract, whereas in some of those with late onset that tract contained many more "spelling mistakes" in the form of CAAs interspersed among the CAGs.



Not all of the molecular alterations that are associated with the HD disease process drive it, said **Juan Botas** (Houston). Some are compensatory and some are noise, and the three categories have to be distinguished. His group tries to do so by conducting comparative analysis of human and model systems. For each gene whose expression is known to be altered in the human HD brain, they either mimic or antagonise that alteration in the brain of a transgenic fruit fly that carries the human mutation, and observe the effects on the disease process. They then validate their finding in other models, such as mice or neurons derived from HD patients. To date they have done this for over 300 genes, and they find that alterations affecting synapses and calcium signalling are compensatory, whereas ones involved in the actin cytoskeleton and inflammation are pathogenic. Knocking down disease-driving genes in patient-derived neurons results in lower levels of mHTT, Botas said, apparently by activating an intracellular degradation system called autophagy.

The incidence of cancer in HD mutation carriers is low. This and other intriguing recent findings suggest that

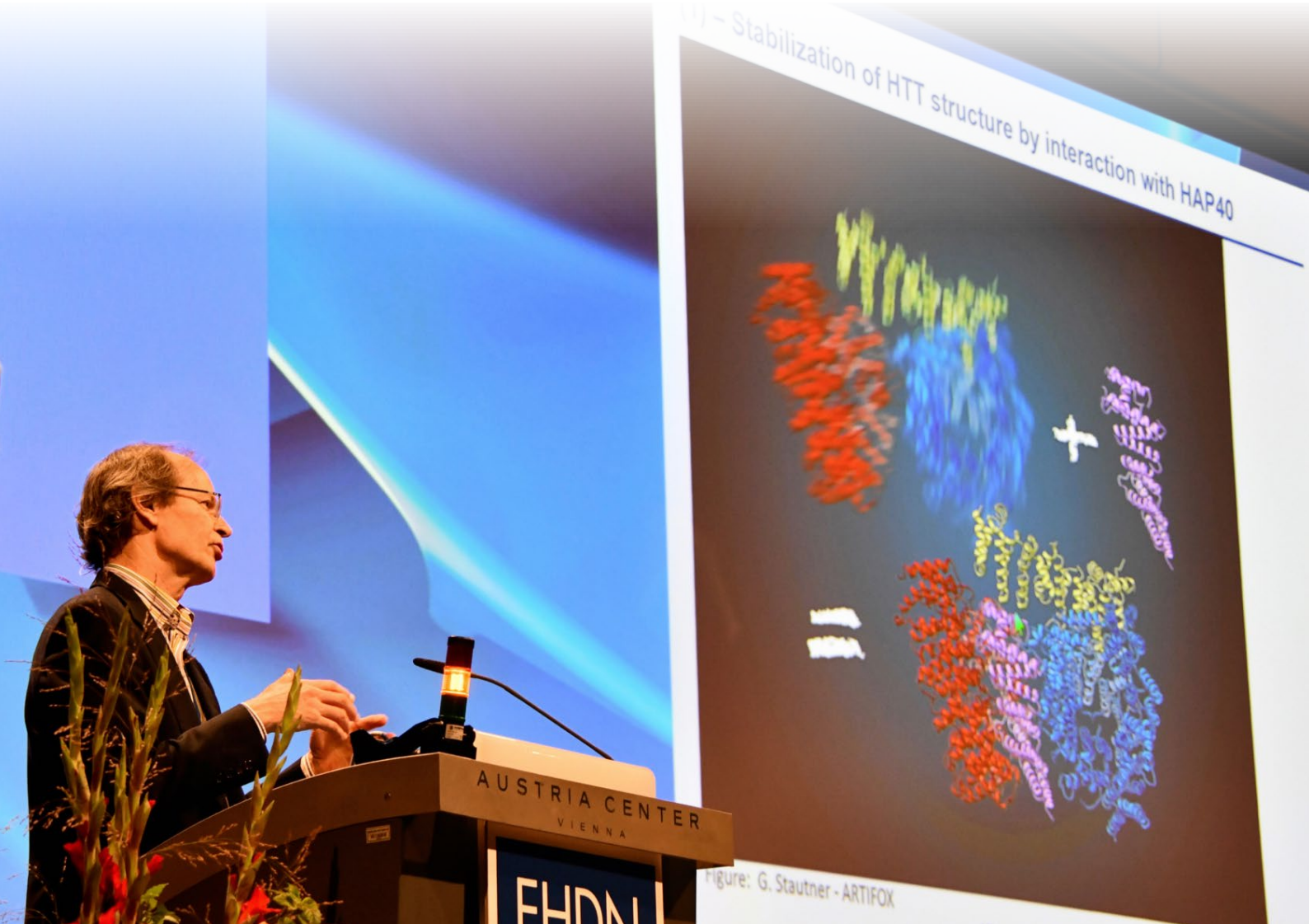
there might be an interaction between *HTT* and certain cancer-related genes. **Elisabeth Singer** (Tübingen) and colleagues are investigating a potential relationship between *HTT* and two genes – *BRCA1* and *BRCA2* – that are associated with inherited forms of breast and ovarian cancer and are known to be involved in DNA repair. Preliminary results of a pilot study she and her colleagues have undertaken suggest that people carrying *BRCA* mutations have a higher proportion of intermediate *HTT* alleles – that is, *HTT* alleles containing a relatively high number of CAG repeats (between 27 and 35) that still don't cause disease.

Ahmad Aziz (Bonn) conducted an EHDN-supported data mining project, using data on more than 3,000 patients participating in Enroll-HD, to try to determine the extent to which the factors determining age at onset and rate of disease progression overlap. He found that about two-thirds of the rate of functional, cognitive and motor decline in HD patients is governed by the same factors as govern age at onset, with CAG count being the most important of them.

Doug Langbehn (Iowa City) helped fill out that picture with findings from the analysis of data from the TRACK-HD and follow-up TRACK-On observational studies, which together spanned six years. He reported that CAG count strongly predicts rate of decline in the premanifest and early stages of the disease – as measured consistently, for example, by the motor and cognitive components of the UHDRS. But the data also reveal three distinct patterns of brain change over the same period – in white matter, grey matter and the striatum – that are differentially sensitive to CAG count and age, and that relate to different components of clinical decline.

The publication, earlier this year, of the structure of the HTT protein to a resolution of a billionth of a centimetre, will also help shed light on how alterations to that protein affect its function. This was the message of

Stefan Kochanek (Ulm), whose group pulled off this feat using cryogenic electron microscopy. They imaged HTT in complex with another, much smaller protein – huntingtin-associated protein 40 (HAP40) – which gives the large, malleable HTT rigidity by binding to it. The images reveal that HTT consists of two main domains connected by a bridge region or pocket where HAP40 sits, suggesting that HTT could act as a hub or dock for other proteins. Like other proteins, HTT is subject to post-translational modifications (PTMs) that affect its function, such as phosphorylation or the addition of a phosphate. Previously, researchers had to try and understand the effects of PTMs by looking at their positions on two-dimensional depictions of HTT. Now that they can see it in 3D, Kochanek said, they will have a much better idea of how those PTMs potentially interact.



What is quality of life?

In 2018, the Economist Intelligence Unit ranked Vienna first among the world's cities – or at least 140 of them – for quality of life. Its definition of quality of life rests on nine factors including material wellbeing, health, political freedom and gender equality. But the indicators it used wouldn't have captured the small, incremental changes in quality of life that accompany HD. **Aileen Ho** (Reading) described her group's efforts to build a patient-centred psychometric instrument that does just that. The Huntington's Disease health-related Quality of Life questionnaire (HDQoL), as it is called, was described in detail in the last newsletter, and Ho announced that it was now robust, valid and ready for use.

Her announcement was timely, given that health economist **Colin Green** (Exeter) recommended that the EHDN include an additional quality of life instrument in the Enroll-HD assessment protocol. Healthcare systems often use a measure called the quality-adjusted life-year (QALY) – a summary measure of health-related quality-of-life – to inform decisions about the availability and funding of treatments. In the Registry observational study, quality of life was measured using a single instrument – a standard questionnaire called the SF-36. QALYs can be calculated from the SF-36 using an adapted measure called the SF-6D, a process that usually involves putting a value between 0 and 1 on health states. However, Green noted that the SF-6D data emerging from Registry indicate relatively little difference in health status between the different stages of HD – hence his recommendation that Enroll-HD complement SF-36 with another instrument measuring quality of life. He also advised the EHDN to consider now – before any disease-modifying treatments reach the clinic – how the framework for economic evaluation is applied across its member countries.

Improving care

Clinicians across the world have been working hard to update HD clinical guidelines in an evidence-based manner, so that patient care may be standardised internationally. **Anne-Catherine Bachoud-Lévi** (Créteil) explained that this was the task of a working group commissioned by the EHDN. Through a process of formalised consensus, the group has drawn up a set of statements that is currently being assessed by patient groups for readability, ahead

of its publication in 2019. **Katy Hamana** (Cardiff) and colleagues have updated the physiotherapy component of those guidelines in light of a systematic review of the impact of exercise and physical activity in HD that they published in 2017. The review found good evidence, for example, that three weekly sessions of aerobic exercise at 65% intensity, alone or in combination with resistance training, improved fitness and motor function.

Clinical research on HD continues, of course, and it continues to inform patient care. Two speakers at the meeting presented their work on dysphagia or impaired swallowing in HD, for example – the topic of an EHDN task force in preparation. In an EHDN seed fund project in which they investigated dysphagia in 73 patients, for example, **Falk Schradt** (Ulm) and colleagues concluded that fiberoptic endoscopic evaluation of swallowing (FEES) was a more reliable method of detecting the problem than standard clinical tests. This was also the conclusion of **Beate Schumann** (Aachen), based on preliminary results from an ongoing study of dysphagia her group is conducting in patients at different stages of HD.

Schumann reported that 80% of the 20 patients they have so far assessed with FEES had impaired swallowing, and that 20% experienced aspiration. That is, they occasionally breathed foreign objects into their lungs as a result of their swallowing impairment – even in the early stages of the disease. Aspiration can lead to lung infections, and in these patients it was mostly silent, meaning that they showed no clinical signs and generally weren't aware of it. Brain imaging data suggest that dysphagia may not be related to motor decline, but rather a distinct symptom dependent on changes in a brain network associated with swallowing. Schumann advised caution in interpreting the findings, however, since the study is still recruiting and the number of subjects tested to date small.

Anne Rosser

Patrick Weydt

Business meeting

Following the 2018 elections, **Lesley Jones** (Cardiff) and **Anne Rosser** (Cardiff) have been re-elected to the EC, while **Jaime Kulisevsky** (Barcelona), **Caterina Mariotti** (Milan) and **Alzbeta Mühlbäck** (Taufkirchen) join it for the first time. **Jean-Marc Burgunder** (Bern), **David Craufurd** (Manchester) and **Berry Kremer** (Groningen) stand down from the EC. **Ahmad Aziz** (Bonn), **Paola Bellosta** (Trento), **Jennifer Hoblyn** (Dublin), **Katrin Lindenberg** (Ulm), **Saúl Martinez-Horta** (Barcelona), **Karine Merienne** (Strasbourg), **Martha Nance** (Golden Valley) and **Daniel Zielonka** (Poznań) join the scientific and bioethics advisory committee (SBAC), replacing **Monica Busse** (Cardiff), **Marina Frontali** (Rome), **Anne Nørremølle** (Copenhagen), **Carsten Saft** (Bochum), **Marta Valenza** (Milan), **Erik van Duijn** (Haarlem), **Christine Verellen Dumoulin** (Charleroi) and **Caterina Mariotti**, who step down. **Anne Rosser** was elected EC Chair and **Patrick Weydt** (Bonn) Co-Chair.

'For animals Huntington's disease is no barrier' was the caption to the winning entry in the photo contest organised by the EHA, which EHA President Astri Arnesen announced on the last day of the meeting in Vienna. Winner Jackie Harrison from Brighouse in the UK took the picture of her brother Mark, who has HD, on a day out in Yorkshire. Jackie explains: 'It captures a small moment of joy in the endless decline and loss that accompany the disease.'

Thanks...

...to all those who made EHDN2018 a success, including the local organisers, the combined organising and programme committee and EHDN central coordination. Thanks to all those departing from the various EHDN committees, who have contributed to the network's growth in size and experience in recent years. Thanks to the European Academy of Neurology for endorsing the meeting, and to additional sponsors F. Hoffmann-La Roche, AOP Orphan Pharmaceuticals, Biogen, uniQure, Voyager Therapeutics, Wave Life Sciences and YuYu Pharma. Last but certainly not least, special thanks go to the CHDI Foundation, without whom neither the network nor the meeting would have been possible.

More photos can be found here.

The full plenary report can be found here.

Dates for your diary

Save the dates for:

- Neuroscience 2018, San Diego, USA, 3-7 November 2018
- World Orphan Drug Congress 2018, Barcelona, Spain, 6-8 November 2018
- Huntington Study Group's HSG 2018: Unlocking HD, Houston, USA, 8-10 November 2018
- 14th Annual CHDI HD Therapeutics Conference, Palm Springs, USA, 25-28 February 2019

Correction: The photo on the front page of the July 2018 edition of this newsletter was wrongly captioned when that edition first came out (it has since been corrected online). The caption should have read: "Picture courtesy of Fabio Festa, Wonderlust Pictures, for the Italian Huntington's Disease Network"