Huntington Study Group (HSG) Conference 2024 – Day 2

Read updates from clinical trials and scientific research on Huntington's disease from Day 2 of the 2024 Huntington Study Group conference

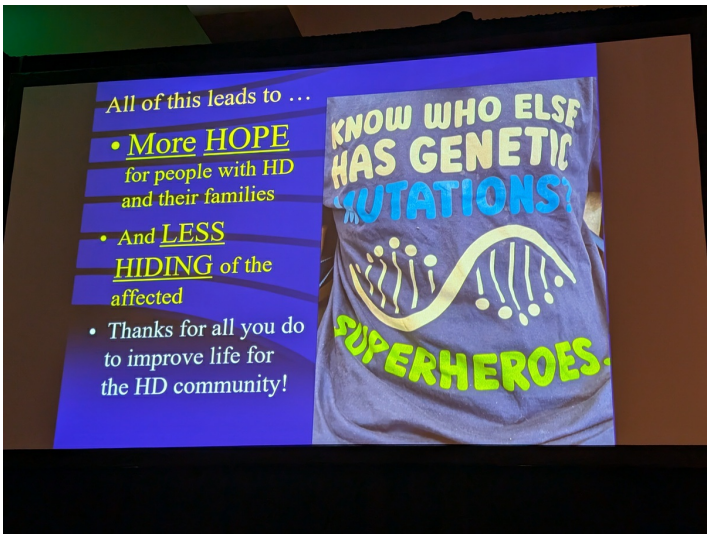

By Dr Sarah Hernandez and Dr Leora Fox **November 12, 2024**

Edited by Dr Sarah Hernandez

We're back for Day two of the 2024 Huntington Study Group (HSG) Conference! If you haven't yet read updates from day 1, you can check those out here. The morning of day 2 is opening with several talks on contemporary clinical challenges in HD.

Palliative care - an extra layer of support

Up first in this session is Dr. Steven Pantilat from the University of California San Francisco, who is an expert in palliative care. Palliative care is medical care focused on improving the quality of life for someone living with a serious illness, like HD.



Dr. Burton Scott has seen some fantastic T-shirts in his clinic over the years from people living with Huntington's disease. He shared one of his favorites that reads, "Know who else has genetic mutations? SUPERHEROES."

One challenge that Steven pushes back against is that people have to choose between quantity of life and quality of life - he says that people can live well and long with palliative care. He presented data from **many** studies in renowned journals, like the New England

Journal of Medicine and JAMA Neurology, relaying the benefits of palliative care. These were clinical trials run on people with cancer who did and didn't receive palliative care.

People who received palliative care had better quality of life, improved symptoms of disease, less depression (without increased prescription of antidepressants), were less likely to get invasive care at the end of their lives, and there were better outcomes for loved ones. There was also higher satisfaction with care, there were fewer days spent in the hospital, and those people who received palliative care had equal or longer lifespans. These are fantastic benefits! Interestingly they were only seen when people worked with palliative care specialists. Steven is making a very strong case for people living with HD to seek out palliative care!

Steven and his team work with his patients to ensure they receive guidance for symptom management, communication, decision making, and psycho-social-spiritual support, realizing that medical care impacts all aspects of a person's life. He urges people to think of palliative care as "an extra layer of support." People may have a care team specific to their illness, like a neurologist, psychiatrist, and social workers, but a palliative care specialist can add to their team to provide extra support.

Steven strongly urges people to be honest, have discussions about what people want for their lives, and not promote false hope. Hope can sustain and allow people to find peace, but only when that hope is grounded in truth.

Wrapping things up, Steven says that **everyone's** life is limited. Who we decide to spend our time with, and how we decide to spend it, will determine if we live a good life. It's up to all of us to ensure that we spend our time here in a way that is meaningful to each of us. He leaves us with final thoughts shared from his grandmother who lived until the age of 93 - live long and live well.

Reflections on treating HD

Our next speaker in this session is Dr. Burton Scott, a neurologist from Duke University. He will share his reflections on treating people living with HD. He began with a story that highlights just how far we've come in the last 30 years, stating there's more HOPE and less HIDING, alluding to a time when HD was frequently brushed under the rug by many families and not acknowledged publicly.

He specifically cited work by Charles Sabine, OBE (OBE = a fancy British honor), who helped bring visibility to HD by organizing an audience with the Pope for HD families in 2017. There, Pope Francis declared that HD families should be Hidden No More. You can learn more about Charles and the work he does with his foundation, HiddenNoMore.

Burton shared some ways that his patients feel that HD care has changed over the years. One point they cited was that the internet has made them feel less alone, giving them an outlet for finding other people from HD families. Finding support and a community to lean on

can be so important!

They also cited HDSA Centers of Excellence in the US, the multidisciplinary care that can help folks get better and expanded treatment for HD symptoms, and expanded Medicare. And, of course, they noted all the research that's going on. There's so much going on in the research space for HD from both academic labs and pharmaceutical companies!

Behavioral changes in young people with HD

Up next is Dr. Katherine McDonell from Vanderbilt University Medical Center who is sharing her experience as a neurologist treating young people living with HD. She is sharing stories of difficult case studies treating folks from HD families where kids have gotten into trouble. It's tough to hear, but these cases can inform the medical professionals in the room today about better treatment of the early behavioral and cognitive symptoms that can disrupt people's lives.

Katherine is promoting awareness of the changes that happen before movement symptoms, sometimes during adolescence. Her experience treating young people with HD has prompted Katherine to focus her practice and research on the behavior of minors from HD families.

She makes the point that diagnosing HD because of motor symptoms is outdated, as psychiatric and behavioral symptoms are some of the first to occur. She urges doctors to update their thinking about when HD symptoms truly begin and to act early.

She feels that if we're going to truly modify the course of this disease, we need more sensitive measures of psychiatric and behavioral changes. Katherine encourages those in the room to work on understanding these changes when people are in Stage 0 (long before typical diagnosis). The staging system she refers to is the HD-ISS, which we've written about before.

> **"Steven says that everyone's life is limited. Who we decide to spend our time with, and how we decide to spend it, will determine if we live a good life. It's up to all of us to ensure that we spend our time here in a way that is meaningful to each of us. "**

Katherine is using alternative tests to measure the behavior of kids at risk for HD. If medical professionals can identify early changes or dangerous behaviors and act to intervene, this approach could make a huge positive impact on the health of HD families. If you want to learn more about the work of Katherine, her study of young people is called ChANGE HD, and it is recruiting.

The talks this morning have been heavy - talking about death, palliative care, and relaying diagnoses for HD. But each of our speakers has conveyed with great emotion how they and their practices have been shaped by the stories of their patients.

Current challenges in clinical trials

Our next speaker is Dr. Cristina Sampaio from CHDI, who will be sharing current challenges in clinical trials. She will break this up into 3 main issues: selecting the right population of people, the choice of endpoints for trials, and duration of follow-up.

She started by talking about the accelerated pathway of approval from the FDA, the US regulatory agency that approves medications. Lots of people are hoping a drug for HD can take advantage of accelerated approval.

But Cristina throws some cold water on this idea, saying that accelerated approval may not bring value to people living with a disease since testing of the drug doesn't end there, so the ultimate outcome of that drug could change. We've seen this before with drugs for Alzheimer's, where accelerated approval led to treatments being put on the market that were later taken off, because more testing showed that the drugs really didn't do what they were intended to do.

We recently wrote about the complex path of the regulatory pathway in research, getting drugs from the lab bench to pharmacy shelves.

With a rare disease like HD, one challenge is that trials need to recruit a narrow population who are at a similar stage of disease, but this is restrictive because the population is already very small. CHDI is taking steps to reshape the Enroll-HD study to address this challenge. Running a trial that doesn't capture the "right" population of people, at a stage of disease that a drug could have benefits for, could prove to be a setback. This is what the HD field experienced with Roche's GENERATION-HD trial.

Cristina emphasizes that the time when people are treated during their disease matters - and many people are asking the important question of how early we should treat HD. If we treat too late, it may have no benefit. If we treat too early, there may be undue risks.

Adding to the complexity of this problem is that we need good biomarkers (biological measurements) to track disease progression at all stages of disease. Finding biomarkers at very early disease stages, before people have noticeable symptoms, has been very challenging. Cristina advocates for finding and using "predictive biomarkers" - biological metrics that will predict how well a person will respond to a therapy.

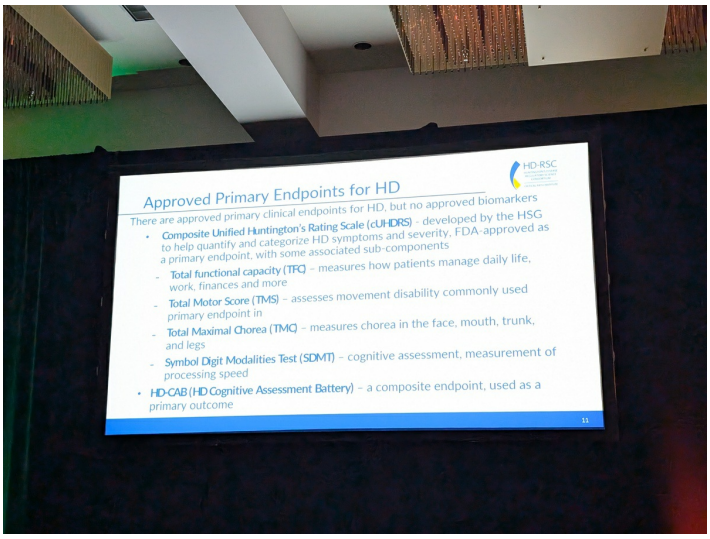
To help find and define some of these biomarkers, CHDI is advancing ENROLL-HD 2.0, which will enhance the original Enroll-HD study that has generated so much important observational data within the HD field.

Clinical trial roundup

The next session focuses on short (very short!) talks from companies currently advancing their medications for HD in the clinic.

Prilenia on pridopidine

Up next is Dr. Michael Hayden from Prilenia. They have been working to advance a potential treatment for HD known as pridopidine, which has been tested in various clinical trials for HD and ALS. Pridopidine works by activating the sigma 1 receptor, a sensor in cells that works to keep brain cells healthy under conditions of stress. The hope is that by activating the sigma 1 receptor in HD, signs and symptoms of HD will be reduced.



Dr. Terina Martinez shared clinical trial endpoints that have been approved for studies on Huntington's disease.

Most recently, Prilenia tested pridopidine in a clinical trial called PROOF-HD. Michael is sharing data from the PROOF-HD trial for a subgroup of people who were not on antidopaminergic drugs. These are a class of drugs typically given to people who have serious depression and psychiatric issues.

Their previous data suggested that people who took pridopidine that were **not** on antidopaminergic drugs may have some improvement in symptoms of HD. The new data they show may suggest that people on low doses of these antidopaminergic drugs may still have some benefit from pridopidine. However, the number of people for which this was tested is small. Michael said the paper for PROOF-HD will be out soon, so we'll go into a deeper dive on this data once that is out.

He also shared that they recently sent a survey out to the HD community for people who were on pridopidine. Feedback from some of those people about quality of life, cognition, mood, and relationships was positive. This is just anecdotal data from the community. As long as these experiences correlate with scientific data, this is great news!

PTC Therapeutics on PTC-518, now known as votoplam!

Dr. Amy Lee Bredlau from PTC Therapeutics is sharing updates from the drug that they're advancing in the clinic, PTC-518. We learned at this meeting that it has a new name: votoplam!

Votoplam is taken as a pill to lower huntingtin. Over the summer (and yesterday) they shared data from people who have been on votoplam for 12 months, which showed that the drug appears to be safe and well tolerated.

They shared that out to 12 months, for people with HD who are taking votoplam, levels of the biomarker NfL remain stable. NfL levels typically rise as HD progresses, so holding levels steady is thought to be a good thing.

Also excitingly, they have preliminary data suggesting that votoplam *may* have a benefit on clinical symptoms of HD. HOWEVER, the trial wasn't designed to look at this and the number of people tested with votoplam was small. A larger trial is needed before we draw any conclusions.

Roche on tominersen

Next up is Dr. Peter McColgan, who is talking about a new set of biomarkers that Roche is using to understand the effects of tominersen in the GENERATION-HD1 study. We've written extensively about the path tominersen has taken.

They're looking at an alphabet soup of biomarkers, called NfL, YKL-40, total tau, p-tau-181, and GFAP. There's a lot of data here (being shown very quickly!). Essentially from their GENERATION-HD1 trial they're finding that at the lower exposures of tominersen, the biomarkers are providing positive information about brain swelling, brain cell death, and other metrics. At the lowest frequency of tominersen tested, there were no increases in the biomarkers to indicate harm to the brain, which is a good thing.

The ongoing Phase 2 trial for tominersen, GENERATION-HD2, is more than 80% recruited, and will close recruitment at the end of the year.

Wave Life Sciences on WVE-003

Up next in this rapid-fire presentation series is Dr. Jane Atkins from Wave Life Sciences, sharing data from the recent SELECT-HD trial. Wave is testing their HTT lowering agent, called WVE-003, that specifically targets the expanded copy of HTT. We recently wrote about an update we heard from Wave this summer.

For people on the drug, there were positive effects, preserving the volume of a part of the brain called the caudate, which is vulnerable in HD. Slowing caudate volume loss could mean that fewer brain cells are lost, but more analysis is needed to ensure that this is really from preserving brain volume and not from a confounding factor like inflammation.

> **"There's so much going on in the research space for HD from both academic labs and pharmaceutical companies! "**

There were a few folks on WVE-003 whose NfL levels rose above that of the control group. In such a small trial it is difficult to say exactly what this might mean, but it's something Wave and others will be keeping an eye on as this program moves forward.

VICO Therapeutics on VO659

Up next is Dr. Scott Schobel from VICO Therapeutics. They're testing their drug called VO659 that acts on the extra CAG repeats within the HTT gene. This means it is designed to target the expanded, disease-causing copy of HTT (and long CAG repeats in other diseases).

Interestingly, VO659 works more potently the longer the CAG repeat length is. They're currently testing this in a Phase I/II trial in people with HD alongside people with another CAG repeat disease called spinocerebellar ataxia.

Today they're sharing safety and tolerability data from the trial in people with HD. So far, this is a very small group - there are only 6 participants with HD. When people had taken VO659 for 29 days, expanded HTT went down by 28% in the fluid that bathes the brain. VICO also has data suggesting that they could dose people every 4 to 6 months with their drug, which is delivered via spinal injection.

Their limited data show that NfL levels remain relatively steady in the fluid that bathes the brain. At day 120, these trends hold, with expanded HTT remaining low and NfL levels remaining steady. This supports a less frequent dosing regimen. Good news!

There have been a few side effects that VICO thinks are related to the spinal injections over time. Importantly, these cleared up after treatment, but they are serious effects so they're important to watch. VICO are continuing to follow all participants for safety and they're developing a plan to address this moving forward. In future safety trials, they'll be testing an altered approach where the drug is given less frequently. Currently they're in discussion with regulators for the next steps for VO659.

UniQure on AMT-130

Dr. David Margolin from uniQure is up next. AMT-130 is a HTT-lowering drug delivered via brain surgery currently beting tested in a Phase I/II trial. We recently heard an update from them over the summer. They have 2-year follow-up data on 21 people who have been treated with AMT-130 in both the US and Europe. People in the trial received either a high or low dose of AMT-130.

Importantly, there are no new safety events to report. They had previously reported a few safety events in the high dose arm of this study that they think are related to high doses of the virus given to this group.

David relayed the exciting news we heard this summer - for people who were given AMT-130, there appears to be a slowing in disease progression. However, this is a *very* small trial that wasn't designed to test the effects of AMT-130 on HD progression. So more data is needed to know if this trend will hold.

It also appears that people given AMT-130 show a decrease in thebiomarker NfL after 2 years of treatment. This could suggest that neurodegeneration is slowing. However, uniQure still hasn't shown trial data related to HTT lowering, which we're eager to see. UniQure are talking to regulatory agencies to continue moving AMT-130 forward. We're excited to hear about the next steps!

SOM Biotech on SOM3355

Our last speaker of this session is Dr. Silvia Panigone from SOM Biotech. She's sharing results from their Phase 2b study testing a drug designed to improve chorea, the movement symptoms of HD. Their drug, SOM3355, has a unique chemical structure compared to other medications currently used to treat chorea. Having multiple available treatment options for chorea will help improve quality of life for people living with HD.

Their Phase 2a trial suggests that SOM3355 is overall safe and well tolerated. Silvia is now sharing data from their Phase 2b study, first going through the study design, which involved groups of participants taking different doses of the drug or a placebo (sugar pill).

There in spirit, a pensive image of HDBuzz Editor Emeritus, Dr. Ed Wild was flashed on the screen. It's seemingly impossible to have a Huntington's disease event without Ed present!

Silvia noted the high placebo effect (improvement with no drug), which shows the importance of having balanced, well controlled clinical trials with lots of different people! Even so, they saw a significant decrease in chorea for people taking SOM3355, with few side effects. SOM Biotech plans to move forward with a Phase 3 trial of SOM3355 for HD.

The path to the clinic

We're back from lunch and hearing updates from Dr. Dietrich Haubenberger from Neurocrine Biosciences on getting drugs to the clinic that are designed for brain diseases, breaking down the traditional and accelerated paths.

As we heard earlier from Cristina Sampaio, Dietrich notes that accelerated approvals aren't full approvals, and regulatory agencies reserve the right to revoke that approval. This has happened for other diseases. He notes that we have to navigate this path in an effective way to increase our success rate. Optimizing clinical trial design requires more investment up front but can ultimately end up moving things along more quickly.

HSG working group updates

In the next session we'll be hearing quick updates from the heads of different HSG "working groups." These are collections of researchers and clinicians with similar interests who meet to work through potential collaborations and solve challenges. Collaborations make science stronger and happen faster! Examples of working group topics include genetics, behavior, neuropsychology, rehabilitation, juvenile HD, digital biomarkers, and social work.

The **digital measures group** is working on finding ways to measure movement, behavior, and thinking at home, to design less burdensome clinical trials using at-home measures and smart devices. They recently got a big government grant to conduct an HD study!

The **neuropsychology working group** recently published guidelines and an educational course for doctors less familiar with HD and neuropsychology. They cover screening for non-movement symptoms and what approaches they can take to intervene.

The **rehabilitation working group** is made up of physical and occupational therapists who help to educate more professionals about HD. They are developing an online course to help prepare staff in long-term care facilities to work with HD-affected residents.

The goal of the **juvenile onset HD working group** is to understand the landscape of juvenile HD care in the US and develop best practices to support people living with juvenile HD and their families.

The **social work working group** strives to better understand the varied and essential roles of social workers throughout the HD community, inside and outside the clinic. They are currently working on a survey to quantify this information and help drive social work education in HD.

The **behavioral working group** creates guidelines for non-HD experts to help care for people experiencing behavioral symptoms of HD. They are currently working on a guide for medical professionals on managing behavioral symptoms in the late stages of HD.

Each of these working groups is operating within its own niche in collaboration with global experts to share research ideas and best practices in care. It's fantastic to see so many professionals committed to educating one another about HD!

Biomarkers and endpoints

Clinical trial endpoints

> **“Optimizing clinical trial design requires more investment up front but can ultimately end up moving things along more quickly. ”**

Up next are Drs. Terina Martinez, Lauren Byrne, and Nicola Hobbs who will be talking about biomarkers and endpoints in HD trials. First Terina is talking about endpoints in trials. Terina is part of the Huntington’s Disease Regulatory Science Consortium, or the HD-RSC. They’re working to lead collaborations that accelerate advancements of HD therapies to improve the lives of all those affected by HD.

The HD-RSC is working to identify the unmet needs, determine clinical meaningfulness, and articulate in regulatory science terms endpoints for trials. Essentially, they work to figure out what data is needed to inform regulatory decision making so that we can get drugs approved for HD. A lot of thought goes into how they determine which endpoints should be used in clinical trials!

She makes the point that if research progress allows us to treat HD earlier, this will require the addition of new primary endpoints as well as the inclusion of biomarkers - biological measurements that change as disease progresses.

Biomarkers in biofluids

Next in this session is Dr. Lauren Byrne, who is telling us about fluid biomarkers. There are various biological fluids that could contain biomarkers, like blood, urine, and even tears! Lauren is primairly focused on biomarkers that exist in cerebrospinal fluid, or CSF, which is the fluid that bathes the brain and spinal cord.

Lauren has done lots of work looking atNfL, which is the biomarker released from dying brain cells that increases as HD progresses. She’s looked at tons of samples where she sees these increases not only in CSF, but also now in blood.

She’s sharing details about how NfL tracks in boxers, which gives an example of the dynamics of this biomarker in healthy brains where there is acute damage to the brain. It takes 6-9 months for NfL levels to return to baseline in these people without an underlying brain disorder. Understanding how NfL levels are increased and decreased naturally in healthy brains is important for understanding the natural dynamics of NfL as a biomarker.

NfL has also been examined in other brain diseases that have available medications to slow the progression of disease, like SMA where nusinersen has been approved. This gives us a clue about how NfL may change in HD trials.

Lauren is now highlighting data from recent clinical trials that have looked at levels ofNfL. For some trials, like Wave’s WVE-003, there seems to be an elevation in NfL, which is important to watch and understand. For medications that require brain surgery, like uniQure’s AMT-130, there’s an expected increase in NfL because brain cells are inevitably damaged with brain surgery. The important part is that this is transient, and NfL levels drop back down to baseline over time.

Lauren has moved on to talking about biomarkers in blood. Some researchers are looking at somatic instability in blood, which can be detected with new techniques. This could be used as a non-invasive way to measure how new treatments affect CAG repeat expansion.

Biomarkers from brain scans

Last in this session is Dr. Nicola Hobbs, who is talking about imaging biomarkers, such as MRI. Imaging methods can provide data on brain volume to give us clues about brain cell loss. Nicola's team uses different imaging and statistical techniques to visualize brain changes and link them to the development and progression of HD symptoms. This can help with selecting participants at very similar disease stages to run informative clinical trials.

She also details some of the main challenges with using MRI to measure brain volume for HD. Firstly, interpretation can skew results, particularly when there is brain swelling. So changes in the MRI can't always be correlated with brain cell loss.

Secondly, side effects could confound therapeutic effects. For example, drugs that change the size of the ventricles (the fluid filled sacs in the middle of the brain) could affect how brain volume is analyzed.

Lastly, Nicola questions how much change in brain volume is needed to define changes that are clinically meaningful. No one has the answer to this question yet, making interpretation of these MRIs challenging.

Beyond the scientific challenges, there is a need to convince regulators that clinical trials should use brain imaging as a measure of whether a drug is working. The HD-RSC consortium discussed by Terina is helping to push these ideas forward from a regulatory perspective.

Thanks for following our coverage from day 2 of the HSG conference! We'll be back for tomorrow's family day where research and clinical sessions will be tailored towards non-scientists and HD community members.

The authors have no conflicts of interest to declare.For more information about our disclosure policy see our FAQ...

GLOSSARY

spinocerebellar ataxia A family of diseases which result in characteristic movement disorders. Many types of spinocerebellar ataxia are caused by the same type of mutation as HD – a CAG expansion.

CSF A clear fluid produced by the brain, which surrounds and supports the brain and spinal cord.

neurodegenerative A disease caused by progressive malfunctioning and death of brain cells (neurons)

clinical trial Very carefully planned experiments designed to answer specific questions about how a drug affects human beings

observational A study in which measurements are made in human volunteers but no experimental drug or treatment is given

inflammation Activation of the immune system, thought to be involved in the HD disease process

therapeutics treatments

juvenile HD Huntington's disease where symptoms begin before the age of 20.

ventricle Normal fluid-filled spaces within the brain.

CAG repeat The stretch of DNA at the beginning of the HD gene, which contains the sequence CAG repeated many times, and is abnormally long in people who will develop HD

biomarker a test of any kind - including blood tests, thinking tests and brain scans - that can measure or predict the progression of a disease like HD. Biomarkers may make clinical trials of new drugs quicker and more reliable.

Receptor a molecule on the surface of a cell that signalling chemicals attach to

placebo A placebo is a dummy medicine containing no active ingredients. The placebo effect is a psychological effect that causes people to feel better even if they're taking a pill that doesn't work.

somatic relating to the body

chorea Involuntary, irregular 'fidgety' movements that are common in HD

magnetic resonance A technique using powerful magnetic fields to produce detailed images of the brain in living humans and animals

HTT one abbreviation for the gene that causes Huntington's disease. The same gene is also called HD and IT-15

NfL biomarker of brain health
