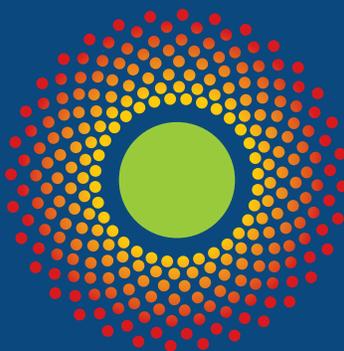


Enroll!

Updates from the Enroll-HD
global community



INSIDE THIS ISSUE:

Dawn of a New Era
HD's "Other" Genes
Q&A: Grzegorz Witkowski

SPRING 2015

THE GET-TOGETHER IN SAN DIEGO

This clan participates family style, turning their annual study visits into a chance to catch up

In 2008, Shelly Meadows got the news that her uncle had just been diagnosed with HD, a disease she knew nothing about. She hung up the phone and went straight to her computer, and what she learned online scared her. If he had the gene, and it ran in families, then did that mean she and her other relatives might also be at risk? It was basically the first time anybody in her extended family had heard of HD, and nobody yet understood what it meant.

Meadows found out online about the HD Centers of Excellence and started calling around in the state of California, where she lives. The first person to answer the phone was Jody Goldstein, a coordinator at the HD center at the University of California, San Diego (UCSD). "We talked for a couple of hours," says Meadows. "I was taking notes and notes." It was the beginning of a relationship that would last for years and come to include much of Meadows' extended family.

Meadows' mother and aunt, both sisters of Meadows' newly diagnosed uncle, wanted to get tested, so she traveled with them to UCSD. "We felt we were in good hands," says Meadows. "They had a whole team explaining things. They were very professional." Both sisters had the HD gene, so other members of the family decided to get tested too. They were scattered across California and the western states, but they gravitated toward the San Diego center and Goldstein, who made them feel at home.

Goldstein told them about COHORT, the long-term observational study that came before Enroll-HD. For many in the family it seemed like a good way to learn more about HD and get involved in research.

Because quite a few had to travel long distances to the San Diego study site, they decided to coordinate their study visits, turning the annual visit into an informal family get-together. "In the beginning it provided a sense of security—we're all in this together," says Sarah Weber, Meadows' cousin. "Everybody wanted information, and everybody was blindsided by the disease. This was an opportunity to do it all together."

They kept up this pattern for years: At some point in July, the family would convene in southern California. Weber flew from Idaho to her mother's house in central California, and the two drove down to stay with her cousin in southern California. Meadows' and Weber's aunt, Sherry Campbell, also has the HD gene. She'd fly in from Tucson, and a few other cousins and sisters would also join them.



The extended family at their San Diego study visit.

En route to San Diego, they'd catch up. "When we get together, we have fun," says Meadows. "It's just how we are." They'd also practice answering questions they remembered from the previous year's tests—counting backward from 100 by 7s, for example, or quizzing each other on how many words they could name that started with the letter A or S (one of the questions on the COHORT cognitive exam).

Within a few years a dozen or so people from the family were involved, so the team in San Diego would book them all together, even bringing in staff to do some tests on Sunday. "They really bent over backwards for us," says Meadows. They'd order pizza for lunch, and make a day out of it, hanging out in the conference room, doing crossword puzzles and using the center's Internet connection. The family is outgoing and gregarious, so the atmosphere was light. "They made it like a party," says Campbell. "It was very easy, and nice."

Goldstein, now at the University of Rochester Medical Center, says that she and UCSD neurologist Jody Corey-Bloom, MD, PhD, were determined to make the visits as convenient as possible for all study participants. The team would shift appointments around in order to make sure that people who worked could come in after work or on weekends, she says. "It's really making research possible for the families."

Sticking with the study

They now realize that even though nobody recognized it at the time for what it was, HD had affected previous generations. Campbell's father (Weber's grandfather) became ill-tempered toward the end of his life, and he also had chorea, says Campbell. But he wouldn't go to the doctor, and the family thought it

was something like Parkinson's disease. He lived until the age of 85. His mother—Campbell's grandmother—was also erratic in her old age. But she had diabetes, and the family assumed that was why her personality changed.

Last year, the group that made it to San Diego for Enroll-HD was smaller. Four of the six siblings in the older generation have the HD gene, and some are starting to have difficulty with symptoms. Other family members have small children at home, or jobs that make it difficult to take days off and travel to southern California. And even though the camaraderie of family makes it easier to take, the visit might feel like a reminder of what the future might hold.

"When we get together, we have fun," says Shelly Meadows. "It's just how we are."

But some in the family are determined to stick with it, and they've already picked a date this summer for their study visit. Weber has not been tested and does not know her gene status, but she believes it's important to volunteer for research nonetheless. She says that being involved in research has made her more optimistic and less frightened of HD. Weber is now a clinical trials research champion for the Huntington's Disease Society of America for the state of Idaho, where she's involved in educating families and

letting them know about studies that might be coming up.

"I feel lucky that we have a group of our family going," says Weber. "It definitely makes it more fun than it could be." It's not easy to confront the reality of HD, but for her, and for many of the other people in her family, having more information about the disease and volunteering together for HD research makes it a little bit easier. "It's not a positive thing, but there are positive aspects of it that can come from it if you're willing to get involved." 

YOU DON'T HAVE TO KNOW

You can volunteer for Enroll-HD even if you haven't been tested and don't know your gene status. Sarah Weber joined Enroll-HD along with her other family members despite not knowing whether she carries the gene, and she's glad that she did. "For me personally, I think there's no way we'll fix

the disease unless we have stuff like this happening," she says.

If you don't want to find out about your gene status, Enroll-HD keeps all research gene testing results confidential. Your gene status will not be included in your medical records, and

even the staff and doctors at your clinic will not know your result. Your gene status is tested anonymously, associated only with a code that can't be accessed by people at the site. The study needs to include gene-negative people as a comparison group, so whether you have the HD

gene or not, your data will be useful, and your confidentiality will be protected. The only difference is that you will not be notified about clinical trials for new drugs or therapies intended to prevent or treat HD.



Weber

DAWN OF A NEW ERA

Despite recent disappointments in drug research for HD, there are new rays of hope

The beginning of 2015 was a turning point for drug trials in HD—the end of one era, and the start of a new one. Last year, two of the longest-running trials of drugs for HD ended in disappointment. But this year, five major clinical trials for HD drugs are either underway or almost ready to launch, including the first tests of a new wave of HD drugs. These new trials build upon what's been learned about the disease. Most of them precisely target specific areas or processes in the brain, and some are using new sensitive measures that can indicate when a drug is working. One was even designed to directly counteract the mutant protein that causes HD.

Many HD researchers think that with this new knowledge, trials are more likely to succeed. "If there were no other trials, I'd be feeling down right now," says Jeff Carroll PhD, an HD scientist at Western Washington University in the US, who is himself gene positive. Instead he is guardedly optimistic that these trials will either identify effective treatments or at least generate lots of valuable information that can lead the way towards an effective HD treatment. "It's a new era in terms of the drugs being tested, and in terms of the quality of the data we can collect," he says. The knowledge gained from each trial makes the subsequent ones more efficient. Improvements such as more sensitive tests and better designed trials that quickly recruit participants at the

most appropriate stage of their disease should make it easier to find out faster whether a drug is working. That way, volunteers only have to stay in a study for six months or a year rather than for many years in a row.

"We know so much more now about HD biology," says George Yohrling PhD, Senior Director of Mission and Scientific Affairs for the Huntington's Disease Society of America. "Our understanding of the biology has progressed to where we're testing better hypotheses."

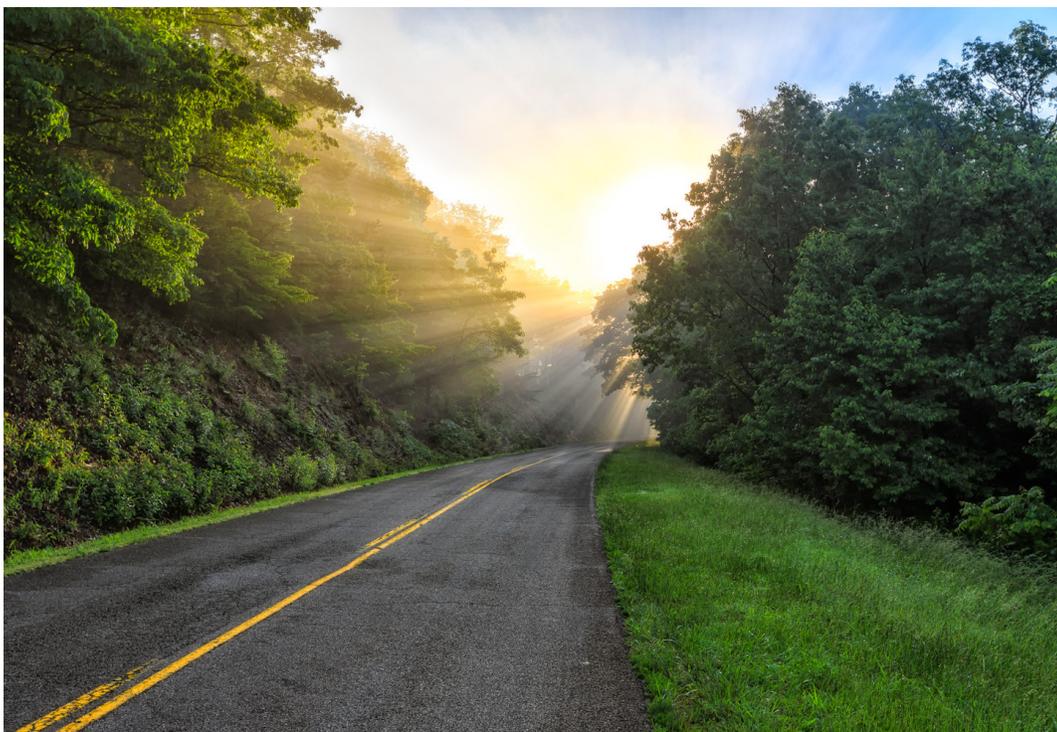
Good news and bad

CREST-E and 2CARE, the two long-running studies that ended in 2014, were both based on the idea that since HD seems to cause energy deficits in brain cells, helping cells produce more energy might improve symptoms. It's a reasonable idea, and both compounds in these studies, coenzyme Q10 (or CoQ10) and creatine, are familiar dietary supplements that are thought to be fairly safe. But their influence on cells is very broad, rather than the kind of precise treatment that many researchers think will be necessary to make a big difference in HD, and neither of them helped. "They're more generally like topping up the gas

tank, as opposed to finding out where the leak is," says Carroll. Some researchers weren't convinced that either compound could actually penetrate the brain's natural defenses and get inside brain cells to change how they function.

If there's any good news it's that at least both of these studies produced clear and definitive answers—they didn't work. The much better news is that a number of other important drug trials also launched in 2014. The LEGATO-HD study launched in November 2014 to test laquinimod, a drug that is intended to

5526
PEOPLE
CURRENTLY
SIGNED UP
FOR ENROLL-HD
IN 11 NATIONS
AS OF APRIL 7, 2015



reduce the inflammation in brain cells that makes them function poorly and eventually die off. It is scheduled to enroll 400 people and finish in 2017. The Pride-HD trial, which enrolled its first volunteer in March 2014, is testing pridopidine, a drug that changes how brain cells use the neurochemical dopamine to communicate. In two previous studies pridopidine seemed to reduce movement symptoms in HD, and this study tests the drug at a higher dose to see if that has stronger effects. This study is expected to be finished collecting data by early 2016.

Also now underway are two trials in the US and Europe testing a phosphodiesterase (PDE10A) inhibitor that is designed to influence brain cell communication and prevent cells from dying. Data for one small trial of this drug has already been collected and is now being analyzed; a larger study is still recruiting participants in the US, Canada, UK, Poland and Germany. This year should also see the start of a European trial to test deep brain stimulation (DBS), a therapy that uses a tiny electrode surgically implanted into the brain to deliver a small electrical current that changes how brain cells function and may improve movement as well as mood and cognition. Although it sounds like science fiction, a similar therapy is used fairly routinely in Parkinson's disease to help with movement control, and a previous small study in Germany had promising preliminary results for HD.

"We're clearly at a phase where these trial announcements are going to come much faster than in the past," says Carroll. And the more trials that are up and running, the more likely

The more trials that are up and running, the more likely one is to succeed.

one is to succeed.

Still in the works is the official start of the Isis Pharmaceuticals study of antisense oligonucleotides (ASOs), a trial that many in the HD research community have been particularly eager to see. Expected to launch later in 2015, this study tests ASOs that are designed to reduce the amount of huntingtin protein (the product of the HD gene) in the brain. This would be the first test of so-called huntingtin-lowering therapies, an idea that has been discussed for a long time in the HD community and shown promise in mouse models, but has not yet been tested in people. Several other approaches to reducing huntingtin are already in advanced development. "We're optimistic that it will be the first of many trials to lower huntingtin," says Yohrling.

The best way to put it might be that 2014 combined setbacks with new horizons. In a blog post last November on the website HD Drug Works, patient advocate LaVonne Goodman, MD called 2014 a "yin-yang year," since it brought both failures and the launch of promising new approaches. And 2015 may turn out to be not so different, calling for a mix of realism and optimism. "The HD community is pretty realistic," says Goodman. "Disappointment is OK, if you can get up from it. And I do think the community will rebound."



FAST FACTS ON 2015'S LARGER CLINICAL TRIALS

NAME	THERAPY	HOW IT ACTS	WHAT STAGE?	WHEN WILL IT END?
LEGATO-HD	laquinimod	reduces inflammation	Phase 2	2017
Pride-HD	pridopidine	changes cell communication	Phase 2	2016
Amaryllis	PDE-10A inhibitor	changes cell communication	Phase 2	2016
Isis	ASO-HTT-Rx	huntingtin-lowering	Phase I	Projected to start in 2015
HD-DBS	Deep brain stimulation	electrical stimulus	N/A	late 2016

HD'S "OTHER" GENES

A study uses thousands of patient samples to search for genes involved in HD

People often talk about HD in black-and-white terms: You either have the gene or you don't. If you do, people say that your 'repeat length'—the number of extra CAG segments in your HD gene—determines how early or late you will get signs and symptoms of the disease.

But HD is not really that simple. Two people with identical repeat lengths may wind up with very different HD experiences, and one might start to be affected years or even decades later than the other. That difference means that something else—other human genes and environmental factors (like lifestyle, diet, environment, etc.)—must be partly determining the 'age of onset'. And the fact that identical twins with HD tend to become sick at almost exactly the same age implies that genes are playing a big role.

To understand this better, an international team of researchers is now analyzing how the other genes in our DNA influence the course of HD, speeding it up or slowing it down and changing the age of onset. "Our study is aimed at finding those genetic factors that make onset even earlier or later than you'd expect based on the length of the CAG repeat," says Jim Gusella, PhD, director of the Center of Human Genetic Research at Massachusetts General Hospital in Boston, USA. Gusella was part of the consortium that identified the HD gene in 1993 and is now central in this new era of research.

If the international team that Gusella is part of can identify genes that postpone symptoms of HD, that will mean two things. For one, it shows that changing the course of HD is possible. Second, identifying genes that delay the onset of symptoms could open up new areas of human biology that could possibly be altered to postpone HD, perhaps for a long time. "You may be able to design a drug that does that same thing, but has a much bigger effect," Gusella says.

It's no simple matter to identify the genes that are most important because many different genes probably have small positive and negative influences on the age of onset. Just by chance, any one person likely has a few that postpone symptoms and a few that hasten symptoms. "You have to scan all the variations in an individual, and compare them in a large number of individuals to find the regions that correlate well," says Gusella. Since 2008, the researchers have analyzed millions of small variations in 4,000 people with the HD gene—including volunteers from REGISTRY, the study that preceded Enroll-HD

WHY OTHER GENES MATTER

Your CAG repeat length—the number of extra repeated segments in the HD gene—is related to when you first have symptoms, but it only accounts for about half of the variability in the age of onset of HD.

What that means is that if one person is first diagnosed with HD-related movement problems at age 48, and another person first gets the symptoms at age 63, only about half of the 15-year difference between them can be chalked up to the differences between their CAG lengths. The other half of the difference must be due to other genes and environmental factors, such as lifestyle (sleep, diet, exercise, stress levels, etc.) that are currently being investigated.

in Europe—to look for patterns in genetic variation in people who have an early or late age of onset. They're casting a wide net, looking across the whole genome.

With this data they've zeroed in on 46 regions of the human genome that have variations that seem to be connected to the age of onset. Other groups are also trying to understand how these regions might affect the health of people with the HD gene. The next phase of research will narrow it down further. "We're in the process of hunting down the exact genes," says Seung Kwak, PhD of CHDI. They're now analyzing samples from at least another 4,000 people, and intend to include more in the future—including samples from Enroll-HD participants.

The payoff for this project is potentially huge: knowing what already affects the way HD unfolds, in real life and in living human beings. Rather than rely on tests in mice or other animals, this approach learns from the experiment that nature has already conducted, says Kwak. "There's nothing better than knowing what actually slows the disease in people," agrees Gusella. 

NOW AVAILABLE

The first wave of data from Enroll-HD is now available to researchers, fully de-identified and privacy-protected. Visit the new Enroll-HD website at www.enroll-hd.org for details.



BEHIND THE SCENES WITH... **GRZEGORZ WITKOWSKI**

Poland was one of the first European nations to join Enroll-HD, and now has six sites up and running. Grzegorz Witkowski, MD, PhD, a physician at the Institute of Psychiatry and Neurology in Warsaw, is the Polish language area coordinator (LanCo) for the European Huntington’s Disease Network, which means he acts as an official representative, translator and point person for the operations of Enroll-HD in that country.

How did you get involved in treating people with HD?

In about 2007, I started to get involved in management of patients with HD in our outpatient clinic. My tutor was a doctor who worked with HD patients for about 20 years, including genetic diagnosis.

HD was always very special for me, because it was the first disease I had very close contact with. The burden is so high, not only for patients but for families, and I felt a great need to work both with these patients and these families. At the time there was no special medical support for HD patients in Poland. That is to say, it was all available in our hospital but there were no clear ways of directing patients to all these specialists. I discussed the situation with other specialists such as psychiatrists and physiotherapists who work in the hospital, and it became possible to refer our patients to these specialists if they needed such help.

Who else is involved in HD in Poland?

Another important part of our work is to cooperate closely with lay associations such as the Polish Huntington’s Association, which does a really great job in Poland. I can’t imagine working without cooperation from them. It organizes physiotherapy for patients, social organizations for families, and meetings two to three times a year in which physicians participate. I enjoy these regular meetings, because we can meet a lot of patients and families, and understand their problems. It’s very useful in everyday clinical work.

What was your experience with REGISTRY, the study that

came before Enroll-HD in Europe?

It was a great help for us. In REGISTRY, as in Enroll-HD, patients should visit at least once a year. We have a lot of patients and the structure of the study database helps us to plan visits. Enroll-HD is a whole world study so we can compare how our patients are doing with those in the UK or France or the US. We can compare disease progression, or see if the response to drugs is similar.

How is Enroll-HD going in Poland?

In REGISTRY, we had about 1,000 participants in total. We don’t yet have quite that number for Enroll-HD, but expect to reach it in three or four months. We expect there are about 3,000 to 4,000 with HD in the whole of Poland, so there’s still a lot to do. People say that HD is rare, but it’s not especially rare!



Grzegorz Witkowski

How do you explain the study to people considering volunteering?

It is very important to clearly explain that Enroll-HD is not a drug study. We don’t provide any special treatment, but we will take care of volunteers since we’re knowledgeable about HD. They can always contact us when they need to. The data we receive from this study are serving us

to understand the progression of the disease. So they’re participating in a huge project. They’re members of a huge community that works to better understand the disease.

Enroll! is a publication of CHDI Foundation, Inc., a not-for-profit biomedical research organization that is exclusively dedicated to rapidly developing therapies that slow the progression of Huntington’s disease (HD). As part of that mission, CHDI Foundation sponsors and manages Enroll-HD. More information can be found at: www.chdifoundation.org

Editor: Simon Noble, PhD
Senior Science Writer: Kat McGowan
Layout: Erik Spooner

Enroll! is licensed under a Creative Commons Attribution-ShareAlike 3.0 Unported License. This means that anyone can take the content from **Enroll!** and reuse it anywhere, as long as they mention **Enroll!** and provide a link back to www.enroll-hd.org

