Huntington’s Disease Clinical Expert Prof. Ed Wild Shares Hopeful View For 2025

The HDBuzz team caught up with editor emeritus and Huntington's disease specialist, Prof Ed Wild to hear his thoughts on what 2025 has in store for the Huntington's disease community

By Dr Rachel Harding | January 27, 2025 | Edited by Dr Sarah Hernandez

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The HDBuzz editorial team had a virtual sit-down with HDBuzz founder, editor emeritus, Huntington’s disease (HD) researcher, and neurologist Professor Ed Wild. We laughed, we cried… actually we just laughed. But we also talked about HD research, the deluge of positive clinical trial news from 2024, and Ed’s outlook for 2025. Spoiler alert: it’s a hopeful one!

Big Picture

HDBuzz: 2024 was a big year for HD research, particularly in the clinical space. Which breakthroughs or advances in HD research from the past year are you particularly excited about?

HDBuzz Editors-in-Chief, Dr. Rachel Harding and Dr. Sarah Hernandez, had a (laughter-filled) virtual sit down with with Prof. Ed Wild to discuss all things Huntington's disease research.

Ed: Honestly, I feel a bit spoiled for choice. In the middle of last year, there was a series of update announcements from trials that came more or less back-to-back, and it felt like drinking from a fire hose of good news.

One of the updates I was most excited about, because it's really moved the needle in my opinion, is the uniQure gene therapy trial. It's a surgically injected gene therapy, made of a genetically engineered virus that is programmed to inject its cargo into neurons. The virus turns those neurons into a factory for making a drug that lowers the production of huntingtin protein. The neurosurgical procedure is a substantial undertaking, but if it works, it will be worth it, because it should only need to be done once. It's a high risk, high reward approach, and the first gene therapy that's been tried in HD.

The uniQure program announced that two years in, in a couple of dozen participants treated with the gene therapy, the people who have received the drug appear to be doing significantly better than controls. The team asked if the uniQure-treated patients look better than we would expect them to based on what we know about the history of HD. There appeared to be a significant reduction in the rate of progression! Particularly on functional scores, the patients appeared to be stable over two years. The placebo effect is a powerful thing, but that combination is a really good starting point for the kind of thing that turns into a success.

HDBuzz: Wow, that's encouraging! What about other data and measures that have been shared so far from this clinical trial?

Ed: Another piece of information that came from that announcement in the summer was that the level of neurofilament light (NfL) protein in spinal fluid was lower at the two year time point on average, than it was at the start of the trial for those patients. NfL is released into the spinal fluid when nerve cells are damaged. If NfL goes up, which it does in HD, that's a sign of something bad happening. If NfL goes down, that is generally seen as a sign that we've actually rescued neurons, which is our aim with HD treatments. The combination of clinical signals moving in the right direction and NfL below baseline is what I've been looking for for the past 20 years, and never seen until last year in the uniQure data update.

It's been said that I am sometimes unduly optimistic, and I might be being unduly optimistic here, but I do think this is the best set of results we've seen so far from a clinical trial. It's small numbers and needs to be replicated, but the other good thing about a gene therapy trial is it's kind of automatic - it basically carries on as long as the patients are alive. We just need to keep track of what happens to these patients.

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HDBuzz: There was some other exciting news from uniQure last year. Can you tell us more about that?

Ed: In December, uniQure announced that they'd had a really productive discussion with the FDA, and in my opinion, this produced two pieces of information that I think are really important for the field, with some caveats.

The first is the use of NfL as a biomarker. In other words, an objective measurement that tells us whether a drug is doing what it's supposed to do or not in HD. The use of NfL as a biomarker was given a big thumbs up by the FDA, and the agency said its use would support potential approval of the drug.

The second was the use of a clinical score called the compositeUHDRS (cUHDRS). This score is the combination of scores from different tests, namely Total Functional Capacity (TFC), Total Motor Score (TMS), Symbol Digit Modalities Test (SDMT), and Stroop Word

Reading (SWR). Previously, the FDA was very reluctant to consider cUHDRS because it was new and hadn't been fully tested. But this time around, in 2024, the FDA seemed to endorse cUHDRS as an endpoint, without any hesitation or reservations.

This is important because each person with HD is very different from one another. One person might have a lot of motor and movement problems. Another person might have a lot of cognitive problems. cUHDRS helps capture the diversity of HD and it actually reduces the number of participants needed to complete every trial, by about 40%.

HDBuzz: Can you explain a bit further why cUHDRS might be used over a single measure, such as TFC, when we want to know if a drug is disease-modifying?

Woody Guthrie, perhaps the most famous person to have had Huntington's disease, was a folk musician with a guitar emblazoned with "This machine kills fascists". Reminiscent of Gutrhie's guitar, Ed said, "HDBuzz was always a machine for turning hope into action".

Ed: This is an important point. As an example, imagine someone with HD who's depressed: this might mean they can't work anymore. Then they are treated with an antidepressant, the depression gets better and they may be able to go back to work. However, you haven't dealt with the underlying damage that's ongoing every day in the brain caused by HD. All you've done is reduce the symptoms of depression. But this would move a score like TFC in a favourable direction.

However, if you have really modified the course of the disease, you would expect one or more of the components of cUHDRS to move in the favorable direction. But even that might not mean that the drug is disease modifying. In my opinion, it comes down to two things. One, is mechanism: what do you know about the drug and how it was designed to slow the progression of HD, does it have a proven ability to alter a known mechanism of HD, and in doing so, does it change the cUHDRS in the expected way? And number two, is supporting evidence that you have rescued neurons. That would come under the realm of biomarkers which could be something like an imaging test, which tells you that the brain is shrinking less, or NfL, which I talked about earlier, which is essentially a protein which tells you whether, on average, neurons are dying more quickly or more slowly than before.

NfL is very widely accepted as a biomarker of brain health throughout different brain diseases. If you lower NfL, it's essentially proof that you've rescued neurons. It's really great that all of these new drugs are in the clinic around the time when we're getting the biomarkers that we need. It's been a big focus for me, and it's really nice and gratifying to see these biomarkers actually being used and being given a thumbs up by the regulators.

HDBuzz: So how can we ensure that when we are looking at biomarkers, we are seeing disease modification, not symptom modification?

Ed: The first thing to say is that we actually want both kinds of drugs. We want drugs to slow the disease, and we want drugs that are better at controlling symptoms, particularly something like cognitive symptoms. If I could help improve my patient's cognition, even if

we're not slowing the progression of the underlying disease, that would be a big win.

My view is, this is why we need multiple biomarkers, and we need to never lose sight of the chain of evidence connecting the disease, to the drug, to the biomarker, and what could be messing up along the way. I think when a drug works, all of the biomarkers and the clinical scores will probably move in the same direction, and that then becomes just much more difficult to have happened by mistake.

> **"This is the first year where I feel like we might get to the end of the year with a good chance of a new drug licensed to slow the progression of HD. I don't know which it will be, but my top two predictions will be either uniQure or PTC. "**

For instance, if a drug inflames the brain of a patient, it might cause swelling, and that could look like slowing brain shrinkage. However, that would also probably cause an increase in NfL, because inflammation could damage neurons. We would conclude that we have an imaging marker going in the right direction, but a chemical biomarker going in the wrong direction. Therefore we shouldn't conclude that that was a success. We need to get to the bottom of which of those two measures is telling us the truth. When everything moves in the same direction, it's just much more likely that we've hit the target in the way that we want to.

At the Lab Bench

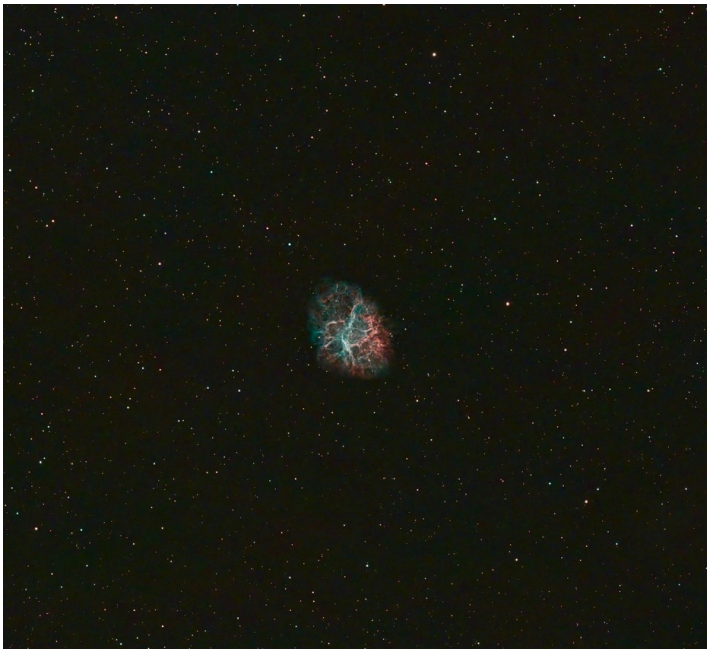
HDBuzz: You're well known for your research in HD biomarkers. Can you talk to us a little bit about ideas that you're interested in exploring in biomarkers as we move into 2025?

Ed: I think that the biggest gap in our biomarker toolkit is an imaging marker that shows us huntingtin protein in the brain. PET (Positron Emission Tomography) scans give us a picture of the brain that lights up where a particular molecule is, and the more of that molecule there is, the brighter it lights up, essentially. These really transformed other fields like Alzheimer's disease, where you can do a PET scan for amyloid and Tau, the main proteins thought to be involved in Alzheimer's disease. You can give a drug and see the amount of these proteins in the brain reducing, and this has given huge support to some of the early therapeutics for Alzheimer's disease. We'd love that in HD!

The uniQure trial is a brilliant example of where that might be particularly useful. Even though the results look good with this drug, one of the reservations is that it's treating a tiny part of the brain called the striatum, which has a volume of about 5 to 10 millilitres, compared to the whole brain, which is over 1,000. Even if you completely save that part of the brain, it's possible that the way the rest of the brain is behaving might obscure the detection of that benefit when you look at scans or even molecular biomarkers.

Certainly, we haven't seen evidence in the uniQure trial that the huntingtin level in spinal fluid has been lowered. We have to assume that that's happening. If we had a PET scan that worked, that was able to show us where the huntingtin is in the brain, we'd be able to see

that the gene therapy had actually lowered the production of huntingtin. That would be solid evidence of target engagement, as we call it. I'd love a huntingtin PET ligand.



The night prior to this interview, Ed was up late taking photos of the Crab Nebula, shown here for your astronomical viewing pleasure. Enjoy!

Image credit: Ed Wild, 2025

I think the next big thing in therapeutic approaches for HD is going to be treatments that prevent the number of CAGs from expanding. And you'll start to hear more and more about drugs targeting things like MSH3, which is a DNA repair protein. But basically, if we change the behavior of those DNA repair proteins, we should be able to keep the CAG count stable, or more stable than it is in the brain.

What we don't have at the moment are any solid markers of whether those drugs are working and changing the CAG count in the brain, except by biopsy which we don't want to do because it injures the brain. Is the CAG getting bigger? Is it stable? How quickly is it increasing? Biomarkers for the process of CAG expansion would be huge for HD.

The closest we can get to the brain realistically is by collecting spinal fluid. But the detection of DNA in spinal fluid is really difficult. We're hoping to combine new DNA sequencing technologies with ways of focusing on stuff in spinal fluid that comes from neurons. We think we might be able to do that with microscopic bubbles called vesicles. Those extracellular vesicles, or EVs, could turn out to be the kind of secret sauce that we need to figure out as quickly as possible, whether CAG stabilizing drugs are actually working in HD.

Clinical Trials

HDBuzz: From which companies should we be expecting updates in 2025?

Ed: This is the first year where I feel like we might get to the end of the year with a good chance of a new drug licensed to slow the progression of HD. I don't know which it will be, but my top two predictions will be either uniQure or PTC.

> **"DNA from the 20,000+ people that are involved in Enroll HD was used to identify these DNA repair proteins as something that is important in the progression of HD. We'd be crazy if we didn't take that evidence from mother nature and make drugs to replicate its benefits. "**

uniQure is expected to give an update in June, which will be the three year update on the same group of patients that we had the two year update from last summer, plus a bunch of new patients. The company has been told that if the three year update is good enough, they will be given accelerated approval by the FDA, a completely unprecedented promise. We just hope that the data delivers and that the agency still takes the same view.

PTC Therapeutics has a drug, now called votoplam, taken as a pill to lower production of huntingtin in the brain and body. We heard last summer that the drug seemed safe and well tolerated, and in contrast to other similar things that have been attempted, there was no sign that it was damaging neurons. On the contrary, it seemed really clean in terms of its safety signal. We expect to hear from PTC, probably late spring, early summer. That's not just an update, that's the full results. The top line results from the first in human trial. I think it's something like 150 participants. It's quite big for a first in human trial, and it's been designed to be big so that if the drug is doing really well, they can go straight to the regulatory agencies and ask for conditional approval.

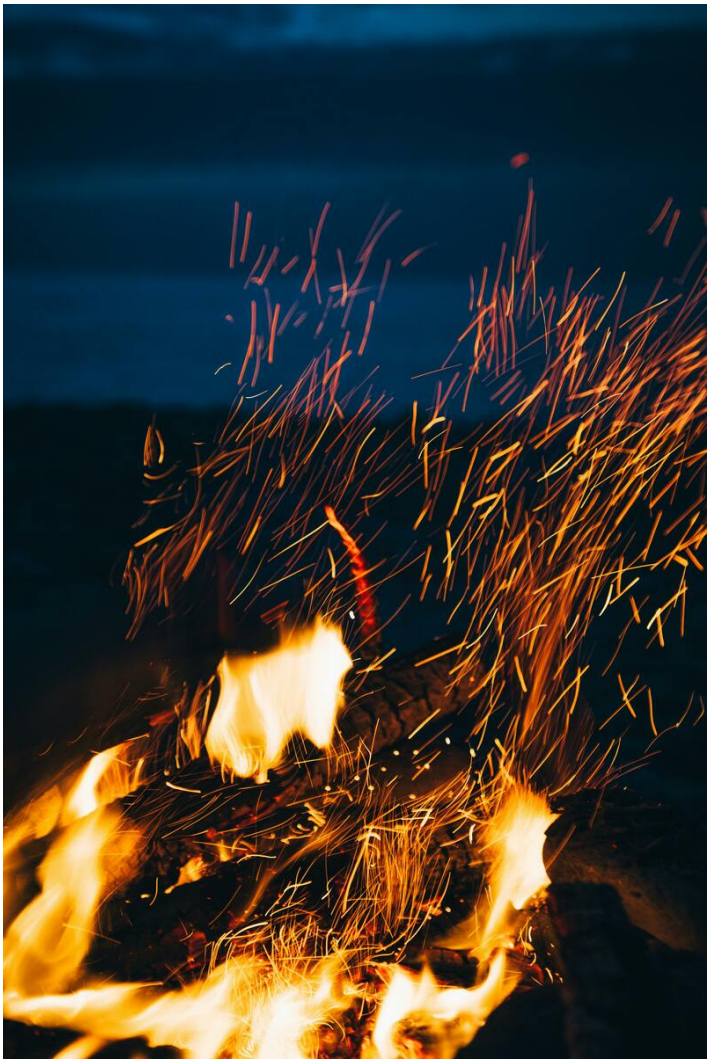
Alynlam Pharmaceuticals is another company that's doing a huntingtin lowering trial that just started in the last few months. What we hope for from Alnylam is actually a period of silence for a while, because they need to start getting patients in. For this kind of first in human program, no news is very much good news. But with a bit of luck, towards the end of the year, we should start to get some top line results.

Slightly below the radar is a drug that we used to hear about a lot,**tominersen, which is the Roche drug**. Following the negative results in 2021, the drug is actually in another trial, now targeting younger people with smaller CAG repeats and using lower doses, in the hope of finding a dose and a group of patients where the drug produces more benefit than harm. We just heard that that trial is fully recruited, but it will be 18 months from that point. We won't hear about anything until probably mid-2026 although it's possible that they will do an interim analysis, and we might hear something this year.

There's been a lot of talk and excitement about these CAG-stabilizing drugs, essentially **MSH3 inhibitors** that are likely to be the first ones that we see reach trials. And there's a couple of approaches we may well see before the end of this year; patients dosed with either a pill or injections into the spine of an MSH3-lowering drug. That will be super exciting, because it's a completely new angle, but it's an angle that came to us directly from

the HD community. DNA from the 20,000+ people that are involved in Enroll HD was used to identify these DNA repair proteins as something that is important in the progression of HD. We'd be crazy if we didn't take that evidence from mother nature and make drugs to replicate its benefits.

HDBuzz: Despite all of these exciting approaches and encouraging data from the clinic, the community has been disappointed before with things not panning out as we had hoped. What is your advice for managing expectations whilst remaining hopeful?



Like a Phoenix rising from the ashes, 2025 is infused with renewed hope, the likes of which the Huntington's disease community hasn't experienced in decades.

Image credit: Iurii Laimin

Ed: I think the reality that's dawned on me is that this is a really difficult problem. We knew it was difficult, and we've had some lucky breaks, but we've also had more than our fair share of bad luck. Things that have gone well for other diseases have turned out to be much more difficult for HD. I've always talked about substantive hope. This was the kind of founding principle behind HDBuzz - that basically, hope is good, and to squander hope, or to let hope go unused or unfulfilled is a tragedy. HDBuzz was always kind of a machine for turning hope into action.

Everyone in the HD community hopes the scientists will develop treatments that work for HD, and we hope that it will happen as soon as possible. That's a great starting point that I recommend for everyone in the HD community. But it's the kind of hope that can be dashed if you hear a couple of pieces of bad news, which is what happened in 2021 with back-to-back disappointing updates from huntingtin lowering trials. Certainly that was very sad and depressing. But for me, because I knew what else was coming through the pipeline and was looking behind the headlines, yes, this was a disappointing result, but what can we learn from it? And the answer in both cases was a ton of stuff. What we learned from the negative tominersen result has been super important in setting us up for a much better probability of success in 2025 and beyond.

I always think of HD as a journey up a mountain. We're trying to climb to the top and when we get there, that's when we've cured HD. But if you just think about that whole journey, it's incredibly daunting, and you'd be crazy to set off up a mountain without a clear plan or a plan of what to do at each stage if something goes wrong. I think the magic ingredient is being informed about what's happening and why we're doing what we're doing. Why are we lowering huntingtin? Why do we care about DNA repair? What does that have to do with CAG repeats? And what does CAG repeats have to do with the disease?

At some point, a doctor is going to be sitting opposite you in a clinic room and is going to slide a consent form across the desk to you, saying, "Do you want to take part in this trial? Here are the risks and here are the potential benefits." If that's your first time hearing about that drug, fair enough, but if you already knew about that drug and why it's been developed and what the history of it is before you entered the room, you're in a much better position to make an informed decision. Breaking down the journey into steps means that if you miss a step, you're only going to be on the one step down. You're not going to be right back at the foot of the mountain.

Taking Action Now

HDBuzz: Recently we covered a paper showing an association between beta blocker use and delayed onset and decreased progression of HD. What are your thoughts on their use for HD based solely on the paper that came out?

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Ed: What I will say about beta blockers is it's an intriguing mystery. This was one of the largest studies that's been done of these drugs and their effect on HD, and the results are pretty robust. Does it mean that people should start beta blockers? Not necessarily, because it's possible that the kind of person that is prescribed a beta blocker happens to be the kind of person whose HD is going to progress more slowly anyway. If there is a direct mechanism, it might be something kind of super boring, like stuff that's good for your blood

vessels, is good for your brain, and that is good for HD.

This could be an extension of the best advice we've been able to give so far, which is, again, quite boring. Don't smoke, don't hit your head against a brick wall, do exercise regularly, have a balanced diet, and look after your cardiovascular health. One of the big things I emphasize is that just because you've got the HD gene expansion doesn't mean that you should stop going to those annoying appointments with your GP, where they measure your blood pressure, cholesterol, and other stuff. Look after your general health.

One thing I do know about HD is that it is very difficult to slow the progression, but it's very easy to accelerate the progression. If you take a bunch of harmful recreational drugs, drink too much, become a professional boxer, neglect your general health, and smoke 40 a day… Don't do any of those things. Do the other things.

Looking Ahead

HDBuzz: What challenges do you foresee for the HD community in 2025?

Ed: Science is amazing at producing breakthroughs and treatments that work. And the nature of science is that it just doesn't give up. If we have a problem, we're going to keep coming up with new ideas, refining them and testing them until something works, and all you have to do is wait, and sooner or later, there will be drugs that work for HD.

Unfortunately, science and healthcare operate in the real world. I think the biggest challenges, which we've thought of as largely relating to places like Latin America, will turn out to be challenges everywhere in 2025 and beyond. I think about the United States, which is a beautiful, brilliant country that I love, but there are lots of Americans that don't have access to health care, and certainly would really struggle to get new, innovative drugs like gene therapies, or genetic therapies, which are likely to be quite expensive.

It's in the nature of HD that it drains people's resources, so the people who need the drugs most often end up being the people who can least afford to receive them. That needs to change, if all of this scientific progress is going to be translated into changing people's lives for the better. For HD-impacted families even more than everyone else, it matters whom you vote for.

HDBuzz: If you could summarize the HD space from 2024 in three words, what would you say? What about 2025?

Ed: "Finally, good news" - is how I would summarise 2024 in 3 words. If I was going to do it in emojis, it would be: exclamation point, smiley face, dancing lady.

For 2025, I would say "imminent success (trepidation)"!

The authors have no conflicts of interest to declare. Ed Wild is a consultant for uniQure, Roche, PTC Therapeutics and several other companies focussed on developing therapeutics for Huntington's disease. For more information about our disclosure policy see

our FAQ...

GLOSSARY

Total Functional Capacity A standardized rating scale for function in HD, used to assess capacity to work, handle finances, perform domestic chores and self-care tasks

NfL biomarker of brain health

huntingtin protein The protein produced by the HD gene.

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

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

therapeutics treatments

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.

endpoint A specific outcome or measurement that researchers use to assess the effectiveness or safety of a treatment. Endpoints are predefined before the trial begins and can be either primary (the main result the trial is designed to evaluate, such as improvement in symptoms) or secondary (additional outcomes of interest, such as quality of life or biomarker changes).

neuron Brain cells that store and transmit information

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.

amyloid The main protein that builds up in the brains of Alzheimer's disease patients

UHDRS A standardized neurological examination that aims to provide a uniform assessment of the clinical features of HD