2024: Year in Review

As we begin 2025, we look back on all of the Huntington's disease research news and progress the field has made in the last 12 months.

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As we wave goodbye to 2024, the HDBuzz team reflects on a year marked by significant progress, challenges, and hope. From breakthroughs at the lab bench, advancements in drug development, and both road bumps and triumphs in clinical trials, we have gained new insights into the workings of Huntington's disease (HD), and made great strides towards finding medicines which might slow or halt this disease. Alongside these developments, the HD community has witnessed the power of collaboration, advocacy, and innovation in driving research forward and improving care. This year-in-review highlights the key moments and milestones that shaped 2024 for HD research.

A new generation of voices at HDBuzz

HDBuzz has been a trusted source of unbiased, accessible information on HD research and clinical trials for over 14 years, helping HD families who are seeking answers and want to learn about the latest scientific advancements. This year, HDBuzz founders Ed Wild and Jeff Carroll passed the baton to a new generation of editors, led by Rachel Harding and Sarah Hernandez, to steer HDBuzz through this exciting new era of HD clinical trials and other research.

The HDBuzz team has been busy this year reporting from different Huntington's disease research conferences, bringing you the latest research updates.

Image credit: Meghan Donaldson, HDF

In addition to our new editorial team, we have welcomed many new voices to our writing team, from different geographies, backgrounds, scientific training, and career stage. Having multiple viewpoints represented across our writers ensures that HD families are getting content that spans what the HD field is thinking. This diverse team of writers includes our wonderful competition winners Zanna Voysey, Molly Gracey, Jenny Lange, and AJ Keefe.

Updates from world experts at HD-focussed conferences

The HDBuzz team has travelled far and wide to different conferences and meetings where the latest updates on HD research and progress in different clinical trials are presented by world experts in the HD field from both academia and industry. Many of the updates presented in these meetings are not yet formally published in peer reviewed journals, meaning we can bring you the most cutting-edge data and research on HD.

In 2024, these meetings included the CHDI Huntington's Disease Therapeutics Conference in Palm Springs, the Hereditary Disease Foundation Milton Wexler Biennial Symposium in Boston, and the Huntington Study Group Meeting in Cincinnati. All of these meetings had stellar line-ups of over 100 talks, panels, and discussions about the hottest topics in HD research. We are excited to bring you more updates early in 2025 at the next CHDI meeting.

Basic research

Somatic instability

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A hot topic in HD research in recent years is somatic instability, and 2024 proved a year where many breakthroughs in our understanding of this phenomenon were made. Somatic instability is the tendency of the CAG repeat sequence in the HD gene to expand further in certain cells of the body over time. A theory many HD researchers are exploring is that cells in the brain with more expansions might be more likely to get sick, thus somatic instability could be driving disease. Slowing down or even reversing CAG expansions by manipulating the way DNA is processed and maintained could be the key to unlocking this theory in the clinic.

2024 kicked off with some fascinating studies, investigating how the CAG number changes in different types of cells in brains from people with HD who have passed. Using these precious samples, the scientists could work out exactly which cells are affected by somatic instability, and how this tracks with which cells get sick and die in brains of people with HD

over time. This granular level of insight is helping us unpick exactly what is going on in HD and is only made possible by the selfless decision of people with HD to donate their brains to research after they pass.

CAG expansion is not just a feature of HD, but actually a whole class of diseases called CAG-repeat disorders which include spinal bulbar muscular atrophy and some types of spinocerebellar ataxias, among other disorders. Given the parallels in the genetic underpinnings of these diseases, we learnt a lot about HD this year from ongoing research in ataxias.

Other research teams have been busy this year exploring the exact molecular consequences of somatic expansion in different models of HD. One team found that changes to the CAG number through somatic expansion can alter the way genetic messages are chopped up and reorganised, a process called splicing. Another group looked to see exactly how long a CAG number needs to be in mouse models of HD for cells in the brain to get sick.

Cellular insights

Beyond somatic instability, research teams around the world have been busy exploring other areas of HD biology. A number of teams have been looking at the blood brain barrier, a protective layer which keeps the brain safe but can also make it tricky to get drugs into the brain to treat diseases like HD. Advances in stem cell research mean that scientists can now make models of this barrier from cells in a dish.

Somatic instability, how a CAG repeat might change in some cells over time, was a big topic in HD research this year. Scientists have been busy figuring out how it happens, and how they might design drugs to manipulate this process.

As well as making these barrier structures in dishes, scientists can also make complex 3D organisations of human nerve cells called mini brains. Derived from stem cells, these structures hold great promise for helping us understand HD in living human brain-like organs, and potentially guide a path for cell-replacement therapies.

We learnt a lot about the cool-looking star-shaped nerve cells, calledastrocytes this year too. These cells are important for brain health and seem to play a role in how cells are lost in the brains of people with HD. Again, this research was made possible because of brain donations.

In the pipeline

HD scientists are always looking for innovative ways to track how someone's HD symptoms might be progressing. In 2024 we learnt of a team of scientists who were looking at huntingtin protein levels in tears. Whilst this might sound rather whacky, this approach is non-invasive, unlike taking spinal fluid or blood samples, and could help track HD progression or even how well huntingtin lowering drugs are working.

More surprising twists and turns for huntingtin lowering arose in a study looking atsplice modulators, a class of drugs which change how the huntingtin message molecule is processed and cause levels of the protein to drop. It turns out that some splice modulators also target another protein called PMS1 which is involved in somatic expansion. Treating cells in a dish, some splice modulators seem to alter somatic expansion **AND** lower huntingtin. This could mean these drugs could have a two-for-one effect!

Edging closer to the clinic for HD are manyCRISPR-based technologies. CRISPR is a clever tool which can precisely edit the DNA code. One of the key challenges at the moment is getting the CRISPR machinery into the right cells to make these changes. In 2024, aCRISPR therapy was approved for sickle cell disease. They got around the challenge of delivery by removing cells from bone marrow, editing them in a dish in a lab, and then adding them back later. Lots of researchers are looking to apply this technology to HD, including a team developing tools to interrupt the CAGs.

> **"It's been an exciting year with new companies in the HD drug discovery space getting started with clinical trials. "**

Updates from the clinic

Bumps in the road

Whilst we always hope for clinical trials to give us the positive outcomes we want, it doesn't always work out that way unfortunately. Clinical trials are some of the most complicated, expensive, and risky experiments that scientists can do, and sadly 90% fail overall. Despite these disappointments, there is always a lot that the community can learn from any trial, whatever the outcome, with the large amount of data collected and different hypotheses tested. It also doesn't necessarily mean the end of the road for the drugs in question.

Pridopidine is a drug with a complex history in the HD space. Now owned by the company Prilenia, it was originally designed to improve movement symptoms of HD and was later thought to possibly slow down the progression of the disease. Despite the negative results

from the phase 3 PROOF-HD clinical trial, Prilenia are moving forward to try and get regulatory approval in Europe for the drug. We should know more about the regulator's decision in 2025.

Another disappointment to many was the halting of development of dalzanemdor, previously called SAGE-718, by SAGE Therapeutics. Sage had hoped that dalzenemdor would work to improve thinking and memory problems experienced by people with HD. However, the drug had setbacks in clinical trials for other neurological diseases and unfortunately failed to show cognitive improvements in the DIMENSION trial where the drug was tested in people with HD.

In both instances, we know a lot of folks in the HD community who had participated in the trials felt as though the drugs had helped them, and that experience is completely valid. It could well be that folks in a certain age bracket, with a specific CAG number, or at a particular stage of HD respond better. However, the overall data in both cases did not prove the benefit of taking either drug to be significantly different from a sugar pill.

Sometimes when it rains, it pours! We have had so many exciting updates from different Huntington's disease clinical trials this year.

Moving in the right direction

Despite these setbacks, 2024 was *abound* with positive and hopeful news from other companies who have clinical trials underway. PTC Therapeutics who developed PTC-518, a pill which can be taken by mouth to lower levels of the huntingtin protein, shared an update with data to support good safety of their drug and even some suggestion that certain clinical scores seemed to be improving.

In quick succession, we then received another update on a huntingtin-loweringclinical trial, this time from Wave Life Sciences who have developed WVE-003 which is delivered by spinal tap. In this update, we learnt that their drug seemed to be generally safe, although flags were raised around their NfL data. Wave also reported that the drug appeared to be selectively targeting the expanded harmful form of huntingtin only, not the healthy version. Further, very preliminary data from MRI brain scans seemed to indicate that folks in the trial on the drug had less loss of brain tissue compared to those on placebo.

Another update came just a couple of weeks later from uniQure, about their huntingtin-lowering trials testing their gene therapy AMT-130, given as a single dose by brain surgery. Although we didn't learn about target engagement in this update (i.e. is the drug actually lowering huntingtin), we did find out that the drug does seem to be largely safe in their updated surgery protocol and could potentially be slowing down symptom progression based on some clinical metrics.

Altogether, this was a bounty of positive news! Not to be an HDBuzz-kill but it is important to note that all of these trial updates are interim - not the final data, and the data are from relatively few people, so there is still a way to go to see how each drug shakes out in larger numbers of people with HD.

Although we did not get a blockbuster update this year from the GENERATION-HD2 trial testing tominersen, a huntingtin lowering drug given by spinal tap developed by Roche, we did learn recently that the trial has now completed recruitment. The scientists at Roche continue to pore over the data from the previous GENERATION-HD1 trial, gaining insights into what might work, and what won't, to give tominersen the best shot in this next phase of its development.

> **"None of the progress we have made over the last year would have been possible without *you* - the HD community. "**

New kids on the block

It's been an exciting year with new companies in the HD drug discovery space getting started with clinical trials. Alnylam Pharmaceuticals kicked off their clinical trial investigating their huntingtin lowering drug ALN-HTT02, with the first participant receiving the drug in December this year. Skyhawk Therapeutics began their huntingtin lowering trial in Australia earlier this year and have already shared an update, demonstrating the promising safety profile and target engagement of their drug, SKY-0515.

Vico Therapeutics updated the community about their CAG-repeat targeting drug, VO659, that can lower huntingtin. Because it targets CAGs, this drug can lower proteins implicated in other CAG diseases, including spinocerebellar ataxias (SCA) 1 and 3. Their trial is testing the drug in folks from all 3 diseases - SCA1, SCA3, and HD. There are some concerns about safety that have been attributed to high dosing which Vico plan to alter in the next phase of their clinical studies. However, the drug does lower huntingtin and could prove to be a path for a new therapy for multiple rare diseases.

A sprinkling of approvals

2024 also saw a new drug approval for the HD community. Neurocrine Biosciences developed INGREZZA, which is used to treat the movement symptoms of HD. INGREZZA is the commercial name for Valbenazine, previously approved for treatment of HD. However, some people with HD have trouble swallowing tablets so Neurocrine made the drug in a sprinkle format to be shaken onto food, which was approved by the FDA.

Path to approval

We are edging closer and closer towards hopefully having drugs which will slow or halt Huntington's disease. In the meantime, there are lots of actions we can take to look after ourselves and our loved ones and keep our brains as healthy as possible.

As we edge closer and closer to finding drugs which might slow or halt HD, the field is thinking more about how these drugs might one day be approved and become accessible to the HD community more broadly. The different regulatory agencies which govern these processes are complex organisations, and their role and processes for drug approvals differ by geographical jurisdiction.

Towards the end of 2024, the HD family community met with the FDA to discuss the challenges they face and what they need from new medicines. Representatives from the FDA listened to the lived experiences of people with HD and family members, to better understand the urgency and needs of the community.

Conversations between companies developing medicines for HD and the FDA also moved forward in 2024. uniQure shared that following discussions with the FDA, that they are aligned on the key elements needed for a drug for HD to be approved This exciting regulatory update matters beyond the uniQure clinical trials, as it maps a path forward for other potential disease-modifying drugs in the clinic, which are seeking to slow or halt symptoms of HD.

Learning from observational studies

In addition to the studies where different medicines or interventions are investigated, there are many different observational studies for HD. These collect biographical information, genetic data, and monitor disease progression over time with different clinical tests and biomarker studies. This helps to create a rich tapestry of data so that we might understand how HD impacts a wide range of people over the course of their life.

A very interesting study was published this year based on a wealth of genetic data that showed repeat expansion diseases, a class of diseases caused by DNA expansions that includes HD, are present at much higher incidence than previously thought. This study, and others, pushed back on the common narrative that HD is primarily a disease more common

in people of White ancestry. In fact, HD impacts populations globally. Critical research in the US is investigating the racial disparity in accessing healthcare and healthcare outcomes for Black and Latinx individuals. Identifying these gaps is the first critical step in helping to combat these issues.

> **"2025 is going to be a big year! Not just for HDBuzz, but for HD research as a whole. "**

Historically, many observational studies have focussed on obvious symptoms of HD, such as uncontrollable muscle movements and difficulty with swallowing. Scientists are now beginning to investigate less obvious effects of HD such as social struggles. There is an increasing awareness of how much these less well-recognised signs of HD can impact an individual and their quality of life.

Another study looked to see which drugs people with HD are already taking and how these tally with the way disease progresses. They found that taking the commonly prescribed beta blockers was associated with delayed onset and slower progression of HD symptoms. This super cool finding was made possible by all of the wonderful folks who participate in Enroll-HD, a testament to the power of the huge dataset contributed by so many HD family members, that helps scientists pull out these cool findings.

Taking action now

The end of 2024 has edged us closer to finding drugs that might slow or halt disease symptoms. Some of these breakthroughs seem tantalisingly close but as we cheer on the HD scientists and clinicians driving these developments forward, there are lots of actions we can take in the meantime.

Many members of the HD community are helping to drive this science forward by participating in clinical trials, observational studies, and surveys. None of the progress we have made over the last year would have been possible without *you* - the HD community. There are also practical steps we can all take to keep our brains as healthy as possible, preparing our future healthcare plans and needs, and making choices about family planning.

One thing which became very apparent this year was the amazing acceleration of HD science through the selfless donation folks made of giving their brains to research after they have passed. So many of the stories we have featured this year have showcased breakthroughs that can only be made with these precious samples. If we want to know more about the effects of HD in the human brain so that we can advance treatments, we need to study the human brain. And thanks to generous donors, we now have more studies than ever conducting such experiments.

HDBuzz has been through lots of changes this year with a new editorial team and funding structure, all whilst we report on a spectacular year of exciting research. We couldn't have done it without your support - thank you!

Supporting HDBuzz

The model that funds and supports HDBuzz shifted in 2024. In addition to support from various wonderful foundations, we began accepting donations directly from our readers to ensure the sustainability and growth of HDBuzz. This decision was made with great care and consideration to ensure the continuation of HDBuzz. Despite these changes, HDBuzz has never accepted funding from pharmaceutical companies so that we can maintain impartiality on the research updates and clinical trial news we cover.

Donations support website maintenance and updates, translation of our articles into various languages, travel to conferences so that we can report on the latest research, travel to meetings to present and directly interface with the HD community, and for the time our writers and editors spend reading, writing, developing content, putting together presentations, and presenting to the HD community. Our content will never be behind a paywall and will always be available to all, but if you would like to support us, we are grateful for every penny. We're eager to put all donations to good use and have exciting things in store for our readers in 2025!

Looking ahead to 2025

2025 is going to be a big year! Not just for HDBuzz, but for HD research as a whole. Several major clinical trials are ending soon that will generate conclusive data. In short order, we will have *definitive answers* about certain drugs that could modify the course of HD! So put on your party hat, throw some glitter in the air, and get ready to ring in 2025 with HDBuzz at your side.

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

GLOSSARY

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

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

therapeutics treatments

bone marrow The gooey stuff in the middle of bones, that manufactures blood cells. When eaten, gives dogs a healthy coat and vitality

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

stem cells Cells that can divide into cells of different types

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.

splicing the cutting up of RNA messages, to remove non-coding regions and join together coding regions.

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

CRISPR A system for editing DNA in precise ways

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

SCA Spinocerebellar ataxia, another neurodegenerative disease caused by increased CAG size

NfL biomarker of brain health