How close are we to a cure for Huntington's?

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"It came completely out of the blue," says James*. They had thought it was his father's knees that were the problem – he was never comfortable and was constantly shifting them. "He went to the doctor, and he said, 'You have got osteoarthritis.' So that was put to bed for a few months." But that wasn't the end of it. James's father deteriorated and consulted a different GP, who said, "Don't worry about your knees, why are you moving so much? Why can't you keep still? I'm going to refer you to a specialist." James and his mother started to realise that his father's movements were nothing to do with his knees. That was a smokescreen. The real cause was Huntington's disease.

First characterised in 1872 by the American physician George Huntington, the disease is one of the cruellest, coldest killers on Earth. It's caused by a mutation of the HTT gene, which creates a toxic protein that gradually destroys vast tracts of the brain, eventually removing all the person's mental faculties. This mutated gene is dominant, meaning that only one of your two copies of HTT needs to be faulty for you to have Huntington's. If one of your parents has the disease, there's a 50 per cent chance of you inheriting it.

For those who know they are at risk, life has always been an agonising waiting game. There is no cure, and symptoms on average begin in the mid-40s (it then usually takes around 15 years to kill). Indeed, for more than 100 years after the disease was characterised, those at 50:50 risk of inheriting it had no way of ending the uncertainty until the symptoms started.

It was only around 50 years ago that the condition began to emerge into the light of day. On 3 October 1967, the folk singer Woody Guthrie died in New York from what was then called Huntington's chorea (chorea is the Greek word for dance and refers to the uncontrollable movements made by people with the disease). A few months later, Leonore Wexler – wife of Milton Wexler, a prominent American psychoanalyst – was diagnosed with the same condition.

Milton Wexler and Guthrie's widow, Marjorie, were powerful people, and both set up foundations to support people with Huntington's, raise awareness and stimulate research. But the great pioneer in the search for the disease's cause was Nancy Wexler, Leonore and Milton's daughter. Milton had begun fundraising and mobilising researchers after Leonore's death, work that Nancy then carried on with official positions at the National Institute of Neurological Disorders and Stroke and Columbia University. Charles Sabine, a former war reporter turned Huntington's activist, who carries the mutant gene, is certain that "without the interest of those families – Wexlers, Guthries – we would be nowhere, we would be 50 years back. It would still be hidden."

Indeed, finding the gene responsible was no mean feat: a large population was needed to detect the genetic differences between those with and without Huntington's. So when a large community of people with the disease came to Nancy's attention, around Lake Maracaibo in northern Venezuela, she worked to win their trust. From 1979 onwards, blood and tissue samples from Maracaibo fed the gene-hunting of the US–Venezuela Collaborative Research Project, led by Wexler. Thanks to the Maracaibo families, in 1983 the causative gene of Huntington's was located on chromosome 4, followed by the precise localisation and sequencing of the gene ten years later.

But since then, those with the disease have waited in vain for the next chapter of the story to begin. They have seen many false dawns, but after several decades there's now new hope. A clinical trial targeting the gene is underway, and preliminary results have, for the first time, demonstrated success in lowering the toxic protein it makes.

Families like James's may finally be about to have their futures transformed.

"Phenomenal". "Ground-breaking". A "game changer". So read the headlines when the trial's results went public on 11 December 2017. It's usually wise to take media coverage of medical research with a pinch of salt, but in this instance the scientific community seemed just as excited – if not more so.

"I really think this is, potentially, the biggest breakthrough in neurodegenerative disease in the past 50 years," said neuroscientist John Hardy of University College London (UCL) when speaking to the BBC. "That sounds like hyperbole – in a year I might be embarrassed by saying that – but that's how I feel at the moment."

Sarah Tabrizi, a principal investigator at the Huntington's Disease Centre at UCL and the leader of the trial, is similarly excited: "A ray of hope emerged in 1993 with the discovery of the genetic source of the disease. Since then, we've been telling HD families that treatments will come. Now we have reason to believe that science has caught up."

To some degree, Tabrizi has inherited Nancy Wexler's mantle as the prime mover in Huntington's research. She is passionate, vibrant, a bundle of energy and conviction – and she now has a hectic schedule, taking the good news about this progress across the globe.

Rightly, she is proud. Researchers have been trying to target the mutant HTT gene ever since 1993. They achieved success in mice as long ago as 2000, but it's taken a lot of further work tailoring a drug and evaluating its effect in mice and non-human primates to get to this stage. The breakthrough delivered by this research is the result of 25 years of painstaking work.

The drug in question is IONIS-HTTRx, developed by California-based Ionis Pharmaceuticals in conjunction with researchers around the world. There are many lines of promising ongoing research, but the Ionis drug – a type of antisense oligonucleotide, or ASO – is the first that's suggested it might be possible to suppress the disease. An ASO works by sticking to the messenger RNA that carries the information for making a specific protein from a cell's DNA to its protein-building machinery. Then the ASO destroys the RNA, preventing the protein from being made.

The Ionis team wanted a way to reduce the amount of mutant huntingtin protein that the faulty HTT gene creates, which is what wreaks havoc in the brain. A crucial issue was whether it would be necessary to target the mutant protein alone ("the bad guy", as Tabrizi calls it) or whether a general lowering of huntingtin – both normal and mutant – would work. Tests on mice, run in collaboration with Don Cleveland's laboratory at the University of California, San Diego, proved the latter to be the case.

The next step was to screen thousands of ASOs to find the one most likely to lower huntingtin effectively in people while remaining safe. "I don't like to use the word 'gene silencing', because ASOs don't silence," says Tabrizi. "You're leaving enough huntingtin to cover its functions."

With an ASO selected, the UCL trial then confirmed the drug's safety and its ability, when injected into the spinal cord, to lower huntingtin levels in the cerebrospinal fluid. The excitement of the result lay in its biological effect: its success in lowering the protein in humans was, Tabrizi says, "beyond what I'd ever hoped".

Hope is now high among those affected by Huntington's too. But until a treatment becomes generally available, their options remain limited. There are medications to help manage some of the symptoms – such as depression, mood swings and involuntary movements – but nothing can yet slow its progression.

Confusion and weight loss always appear as the disease takes hold. The journalist Charlotte Raven has been symptomatic for over seven years. She is quite thin, and keeps up good conversation in a strong voice with no trouble, but she can't read any more – "the words just don't go in". As a writer and editor, she's acutely aware of what the disease is doing to her, and she misses the bustle of running

a magazine; planning and coordinated activity are difficult. "I just sit and listen to Radio 4. Dramas I can't take in, but news I can do."

For people like Charlotte and their families, the last great breakthrough was the arrival of testing. A 90–95 per cent accurate test followed the location of the HTT gene in 1983, though it was complicated, needing several family members to make a diagnosis. When the gene was sequenced in 1993, an almost 100 per cent reliable test became available – but for many, this only compounded the misery.

As James says: "When it was discovered, they thought there'd be an influx, but no one's coming through the door. Thinking about it, why would you want to know?" With no cure available, taking the test means a person has the chance of turning their 50 per cent hope into 100 per cent misery at a stroke. Most decide to wait and see. To this day, only around 20 per cent of the at-risk population in the UK have taken the test.

Elisabeth Rosser, a clinical genetics consultant at Great Ormond Street Hospital in London, has some revealing figures on the psychology of testing. The fully reliable test was offered to 80 people in Oxfordshire who had previously tested positive on the 90–95 per cent test. When she asks me to guess how many opted for it, I plump for 10, thinking I'd better aim low. Only one took up the offer.

"They wanted that 5–10 per cent of doubt and hope," Rosser explains, the modest chance that their diagnosis was wrong. Conversely, people who had tested negative before were also reluctant to take the new test: "They feared that their near certainty of being disease-free might freakishly be taken away." But the existence of a treatment would surely change this. Starting treatment before the onset of symptoms is always going to be better.

The main spur to taking the test has been the wish to start a family, and it's here the broader implications of there being no treatment come into focus. Before testing became available, many of those at risk simply opted not to have children – with a 50 per cent chance that their self-denial was unnecessary. Some gambled. But with the arrival of the test, another option became available: pre-implantation genetic diagnosis (PGD). This, though, brings its own difficulties.

PGD involves in vitro fertilisation, with only embryos free from the Huntington's mutation being selected. Since 2013 the NHS has offered three free cycles of PGD to at-risk couples. The proviso is that if successful, it won't fund PGD for a subsequent child. The cost of private PGD – the price of a sibling – is around £15,000.

The test; the wish to have children; PGD; the lack of a treatment – these play out in various permutations in different families. James and his wife wanted healthy children, but PGD normally reveals whether the parent has Huntington's – and James, like many others in families with a history of the disease, didn't want to know. There is a way PGD can do this, using a protocol called exclusion testing. It involves seeing which grandparents an embryo has inherited its chromosomes from. In the case of James, any embryos carrying a chromosome 4 from his father were excluded.

This worked for James and his wife, but there were complications, and they lost their baby at 12 weeks. "It affected my wife quite badly," he says. They waited to try again, but gradually it became clear that this was not going to happen. The issue of James's at-risk status became a problem, and they split up.

James came to decide that if he were to think about entering a new relationship and having children, it would be better if he had been tested. In September 2017, he received his result: he doesn't have Huntington's. He has a clear future.

For Louise and Simon (names have been changed), things started similarly but then took a different course. "We didn't know that HD was in the family until my dad was diagnosed," Louise recalls. She and her sister were now at risk, and the dilemma of whether or not to get tested left them "going round in circles". But, she says, "PGD was one area where we felt we could do something positive – move forward." Like James and his wife, Louise and Simon opted for exclusion testing. This

was successful, and they now have a boy.

But Louise knows she would have acted differently if a treatment had been available: "It's a game-changer. If there was a treatment, I would want to know my status, so I could start ASAP if I was gene-positive."

The way James and Louise and Simon engaged with the options is by no means typical – awareness of the availability of PGD and uptake of all the possible interventions are low. Nayana Lahiri, a clinical geneticist at St George's Hospital in south London, reports that prenatal testing has remained at a constant, fairly low level in the UK since the mutant gene was sequenced in 1993. On average, just over 20 tests have been conducted each year. PGD has become more popular – at least 50 cycles were completed in the UK in 2015 – but this represents a recent sharp rise. From its introduction in 2002 until 2009, the annual number of cycles was never more than 20.

What is evident is that, although the disease is implacable, every family deals with it in their own way. Charlotte Raven had a daughter, Anna, in 2005, just months before her father divulged that he'd been diagnosed. She did decide to take the test, which proved positive, and there followed "years of agony". She "worried about Anna being on her own", so she and her husband decided to have another child. "I remember thinking should I get the embryos tested," she says, but in the end, rather than try to "medicalise everything", she decided to proceed without. As she put it in an article in the Daily Telegraph: "In the event, hope won over apprehension and our son was born, five years after his sister." Both, though, will have to wait until they are 18 to take their own tests to see whether they have inherited the faulty gene.

PGD may help individual families worried about passing on Huntington's, but it can only do so much. Apparently random new appearances of the disease aren't just the result of families hushing it up in the past – its very nature means that it will continue to appear out of the blue.

In a mutated HTT gene, a particular triplet of DNA bases, CAG, is abnormally repeated. With below 26 sets of CAG in each of your two HTT genes, you won't get the disease, but with more than 40 in just one of them, you will – at an age that depends on the number of those extra repeats.

In between lie two grey zones. If you have 27–35 repeats, you won't develop Huntington's, but your children still might, because the repeats are unstable across generations, more often increasing than decreasing if passed down, especially in the male line. With 36–39 repeats, you may or may not get the disease, but either way your children are at higher risk. The tendency for the number of repeats to increase in the next generation is especially marked once you've reached 36.

In the UK, it's estimated there are between 6,000 and 10,000 people with Huntington's, and another 25,000 at risk of developing it. But, if the prevalence figures from a 2016 Canadian study of the borderline cases (36–39 repeats) are similarly reflected here, a further 150,000 people in the UK could pass on a higher risk to their children.

Elena Cattaneo at the University of Milan has mapped the entire life story of the HTT gene – dating back a billion years – to try to get to the bottom of why the number of CAG repeats has this insidious habit of increasing from one generation to the next. The gene's first appearance (with no repeats) was in the single-celled amoeba Dictyostelium discoideum. Two repeats then start to show in sea urchins, and they gradually increase throughout animal evolution.

The repeats are highest in humans, and there is some evidence that a high level of repeats up to the danger zone may enable higher cognitive functions. Amber Southwell, assistant professor of medicine at the University of Central Florida, says that MRI studies have shown that people towards the high end of the safe range (up to 26 CAG repeats) have more grey matter than those with fewer.

Indeed, it's possible that rising CAG repeats on the HTT gene could have been part of an evolutionary process that helped raise humans' mental capacities above those of other animals. This reveals a potential paradox of the disease: that, as Cattaneo and her colleague Chiara Zuccato have

suggested, the terrible destruction of Huntington's could in fact be "an offshoot of a biological process that ultimately made us the human beings we are".

And the rise in CAG repeats continues. "No matter how good your family planning is, we'll never eradicate the Huntington's disease mutation," Southwell concludes. Or, as Charles Sabine puts it, Huntington's is "a disease of the future".

On the day that the UCL trial's success was declared, the Swiss pharmaceutical giant Roche announced that it would take up a $45 million option to move IONIS-HTTRx on to the next stage: a phase III trial involving hundreds of patients over a longer period to assess whether it can reverse symptoms. At this stage, there's only evidence that it combats the cause of Huntington's in humans, not the disease itself – though Ionis and its collaborators have used an ASO to reverse symptoms in mice.

And although the excitement about the result was fully justified, Sarah Tabrizi sounds a note of caution: it will take time to move things forward. "We expect that planning for this study will take about a year, and then it will take several years to enrol and complete. In these studies, if the drug provides clinical benefit in people with Huntington's disease while maintaining a favourable safety profile, Roche will apply for marketing approval." It is this, ultimately, that will decide whether a safe and effective treatment has finally arrived.

Some experts believe the Ionis drug's non-selective approach, lowering both normal and mutant huntingtin, is a gamble. While studies have shown that reducing huntingtin – even knocking it out completely – is well-tolerated in adult mice, Southwell believes the risks haven't been fully explored: "I think you can't really draw a conclusion about this from a nine-month study in mice. We're talking about decades of treatment in humans."

This will be a major concern in the clinical trial to come: will IONIS-HTTRx be safe over many years of use? And what about delivery? Getting the drug into the brain by injecting it into the spinal cord means some parts of the brain are reached better than others. Striking a balance, over decades of treatment, between lowering mutant huntingtin in the right places and not lowering the good protein too much elsewhere will not be easy.

So, other treatment methods are actively being sought. Targeting mutant huntingtin alone is Southwell's preferred approach, but it will require some ingenuity: for all the intricacy of the genetic tools we've developed so far, they aren't very good at counting. Getting them to pick out, say, an HTT gene with 40 CAG repeats and silencing it while sparing a good gene with only 26 repeats is challenging. But there is a way.

Genes are inherited in blocks, known as haplotypes, which mostly travel together on the chromosomes, and the Huntington's mutation has travelled with just a few such typical blocks. This means that you don't have to count the CAG repeats to tell good and bad HTT genes apart; instead you can look for tell-tale variations in the genetic material nearby – individual DNA bases that differ between haplotypes, known as single nucleotide polymorphisms. An approach that uses these to target only the mutant gene is now moving towards human clinical trials.

A further option is AMT-130, a gene therapy being developed by the Dutch company UniQure, which uses an engineered virus to carry interference RNA into cells to silence the mutant gene. This is promising because it could result in a lifetime cure from a single dose, and clinical trials are due to start this year.

Finally, there's another strategy being led by Gill Bates, co-director of the Huntington's Disease Centre at UCL, who was one of the researchers from the 1993 team that found the HTT gene. One thing that makes mutant huntingtin more toxic is a virulent protein that HTT sometimes produces in error. Bates's work is looking at how to stop the production of this protein.

Treatments for other diseases, such as cancer and HIV, often involve more than one agent, so this isn't necessarily a competition. Tabrizi envisages a possible future in which the above approaches and others could be combined: a virally delivered interference RNA could be delivered to the striatum

(a portion of the brain seriously affected by Huntington's), a drug similar to the Ionis one could target the cortex, while a small-molecule drug might mitigate the disease's effects on the body.

But beyond all of these techniques, what we'd really like to be able to do is snip out those accursed extra CAG repeats. The wherewithal to do this is perhaps now to hand, thanks to the gene-editing tool CRISPR. Since its discovery in 2012, it's already been used to target the mutant HTT gene in mice, successfully restoring normal functions. But a major complication is that it targets a particular DNA sequence wherever it finds it in the genome, and there are many other genes with CAG repeats. Unless we can be sure that there will be no off-target effects, CRISPR is risky. And once made, the genetic change is final and any unforeseen consequences cannot be reversed.

So as befits a problem the size of Huntington's, there's lots of promising work underway to try to find a cure. But, notes Ed Wild, a clinical scientist at the UCL Huntington's Disease Centre, "there's a problem of hype in HD press releases". This is why he co-founded the blog HDBuzz – "to propagate a more tempered narrative" around research in the field. (So tempered that Charlotte Raven has another name for it: HDBuzzkill.) For the leading therapy, the Ionis drug, this has meant underlining the necessary timescale for the crucial phase III trial: three to four years is likely, plus the time it would take to license it if successful, so perhaps five to six years in all.

Nevertheless, Tabrizi remains confident. As she notes, families have been promised Huntington's treatments since the discovery of the HTT gene in 1993. "Now we may be able to offer a precision medicine that improves the lives of everyone affected," she says. Others are confident too. John Hardy believes the Ionis drug could be a test case for treating many other neurodegenerative diseases. Even HDBuzz called Ionis's December 2017 results "the best early Christmas present we could have hoped for".

But the last word should go to members of families affected by Huntington's. Understandably, they have been very emotional about the trial's success. James, though excited, is afraid that "by the time they manage to license the trial drug and do further testing, my father will no longer be around". His dad is now in the late stages of the disease.

But for Jessica Wilson, a young woman who has tested negative but has two family members with Huntington's and several others at risk, there is hope: "I can say that I will never be the same as I was before [the disease] surfaced; now I can say that I will never be the same as I was before today, before the news hit. Nothing the world throws at us now will ever be tougher than this has been."

* *Some names have been changed.*