TPWKY	This is Exactly Right.
Jay	My name is Jay and I am 34 years old and I was recently diagnosed with Huntington's disease. My grandfather was diagnosed with Huntington's in his 80s but I don't think he and my grandmother really understood the severity of the illness and its implications for their children and grandchildren. So they never really told us until my father started seeing some symptoms in his 50s. So that's when I found out, I guess I was 28, I'd just been married, you know there's so much optimism and then I find out from my parents that there's this terrible shadow, you know, that's going to be potentially hanging over my life. And it was definitely really, really hard, I'm not gonna lie. Your priorities sort of shift, just trying to maximize the years that you might have with a good quality of life, you know. So I didn't get tested right away, I really wasn't ready.
	But over the years I started to I guess come to a point of acceptance and I also started to see symptoms starting to appear. Things like coordination issues, balance issues also, difficulty swallowing and drinking. So that's how it's starting to affect me and it got to a point where I was ready to be tested. And so I did that I guess a few months ago actually and now I have the official results that I am positive for Huntington's disease. At that point I guess it wasn't as bad as I thought actually to get those words. For me it was I guess a little bit freeing to finally have some solid answers and to know what my reality would be. I'm really lucky to have a really supportive husband with me, he's been a rock for every step of the way, being understanding for all my decisions.
	One in particular is that I feel really strongly that I don't wanna pass this on to my children. I know that's maybe a controversial opinion but I just can't imagine potentially burdening them with the same difficulties that I'm experiencing. So we'll be using IVF, they have this cool technology where they can test embryos and that's the route we'll be taking. But obviously it's also time consuming and expensive and not a guarantee so it's one of the most disappointing things about this diagnosis is one of the few things I really knew I wanted was a baby. And now we can't just conceive the natural way, we've got to go through all these hurdles.
	Another aspect about it that's really difficult is because it's a family disease. I saw my grandfather suffer from it and now my father is suffering from it and now I'm going to have the same symptoms and my aunt also and possibly my brothers. So it's really difficult to not feel like you're being a burden if you want to, you know, share your feelings with your family members and reach out to them without being potentially a burden to them when they are also dealing with this kind of stress and also being a burden to my husband of course. Eventually he'll be caring for me more and more, so yeah it's really, really hard.
Jay's Husband	Hi, this is Jay's husband. Some of the difficult things are trying to explain to, say, my side of the family what's going on, my sisters have their families going along and things like that. And at this point we've had your diagnosis for more than a month but we still haven't found the right time or place or way to even tell our extended families or my family even. I think basically for you it's just your immediate family on one side that we've really talked to about it. But we don't even know how to tell our friends about this because we don't have the words and we don't know how to, I guess. We're not looking for sympathy but we also don't wanna keep it a secret and given that it's not something that can be cured like cancer or COVID, this is something that is not going away and I think that has been one of the really stressful parts. We haven't really figured out a good way to share with those that are even closest to us.

	And I think that this definitely weighed on me at least to have this information and not be able to really talk to people about it yet because we don't know how. And another thing that we've kind of been thinking a lot about is what do we do? Right, unlike some diseases again that do have cures, when do we need to tell our insurance? Because we definitely will want as much of the care to be covered by insurance but that's not something that a lot of people have been able to give us advice on or there's not a good rule book or a guidebook out there because everybody's path with Huntington's is different, then the solutions and how they solve it are all different.
	I think one of the really difficult parts is that Jay's grandfather showed symptoms in his 80s and his path and how he dealt with it was very different than her father who was in his 50s when he was diagnosed and that's very different from Jay who started displaying symptoms in her 30s. And so even when we look for comparisons to how to manage and how to deal with it, we don't have a particularly good role model or something to compare to. We're kind of going at our own pace and in our own direction and hoping that we get it right but also being really aware that we don't have a lot of flexibility, that we have to get it right the first time because all these days are precious.
Jay	Yeah I guess that's definitely a downside of it being a relatively rare disease and like something like cancer, there is just not as much resources, there's not the kind of community that you get when you're diagnosed with cancer, let's say. There's not as much research, not as much funding. So yeah I guess overall I've been trying to just, you know, do it day by day, little by little, some days are good, some days are bad but it's my reality now and you don't really have a choice anymore, right. You just have to... You're out on the train, so you kind of have to deal with it and I guess that's been how I'm trying to look at it. And hopefully I can just keep some optimism as things progress you know, despite what might come.
TPWKY	(transition theme)
Erin Welsh	Thank you so, so much for sharing your story with us, we really appreciate it.
Erin Allmann Updyke	Yeah, thank you.
Erin Welsh	Hi, I'm Erin Welsh.
Erin Allmann Updyke	And I'm Erin Allmann Updyke.
Erin Welsh	And this is This Podcast Will Kill You.
Erin Allmann Updyke	And today we're talking about Huntington's disease.
Erin Welsh	Yes we are. This is just one of a handful of the genetic diseases that we have covered, Erin, right?
Erin Allmann Updyke	Yes it is and it's very different than the other genetic disorders that we've covered so far, so.
Erin Welsh	Yeah. I mean this is a big topic to cover, so.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. So let's maybe get right down to business with business we should cover?

Erin Allmann Updyke	I think that's a great idea. Yeah, the first business as always is quarantini time.
Erin Welsh	It's quarantini time. And this week we are drinking The Marjorie.
Erin Allmann Updyke	The Marjorie.
Erin Welsh	Named for Marjorie Guthrie who was the founder of one of the biggest Huntington's disease advocacy groups in the U.S. now called the Huntington's Disease Society of America, I believe.
Erin Allmann Updyke	Excellent. And what is in The Marjorie?
Erin Welsh	The Marjorie is vodka, orange juice, unsweetened cranberry juice, and a little bit of amaretto.
Erin Allmann Updyke	Excellent.
Erin Welsh	Yeah.
Erin Allmann Updyke	We'll post the full recipe for that quarantini as well as our nonalcoholic placeborita on our website thispodcastwillkillyou.com and all of our social media channels. As always.
Erin Welsh	And the usual business I guess, you know we have transcripts which is thrilling.
Erin Allmann Updyke	Thrilling.
Erin Welsh	You can find those on those on the TRANSCRIPTS tab of our website. And on our website you can also find all kinds of other fun things like a Goodreads list or a link to a Goodreads list, a link to our Bookshop affiliate page, any of the sources that we use in all of our episodes, link to Bloodmobile's music page on Bandcamp, I mean it's all there, just check it out, you'll have a fun time.
Erin Allmann Updyke	It's a very fun time on our website.
Erin Welsh	(laughs)
Erin Allmann Updyke	(laughs) All right. Well this is as you said Erin, it's a very big topic so shall we take a quick break and then dive right in?
Erin Welsh	Let's do it.
TPWKY	(transition theme)
Erin Allmann Updyke	So right up front, Huntington's is a neurodegenerative genetic disorder that is inherited in an autosomal dominant fashion. So what does that mean? It means that this is a disorder that's affecting the brain and the nervous system and you only need one copy of the mutated gene in order to have disease. So that's already different from the other two genetic disorders that we've covered in the past, namely sickle cell and cystic fibrosis.
Erin Welsh	Mm-hmm.

Erin Allmann Updyke	Which are both autosomal recessive so you have to have two copies of a mutated gene in order to have disease. But before we can actually talk about Huntington's disease, I think we need to step back and talk about our genes in more detail than I think we have on this podcast, at least recently. So here's where we'll begin: our DNA is made up of little building blocks like legos called nucleotides which we give letters A, T, C, and G. So three of these nucleotides grouped together form what's called a codon because that is what codes for an amino acid. Well it codes for RNA which codes for amino acids, but we'll ignore that. Okay.
Erin Welsh	Right, right.
Erin Allmann Updyke	When you string a bunch of amino acids together, you get essentially a protein. Scattered throughout our genome, throughout not just human genomes but like every genome, animals, plants, bacteria, we have these short repeat sequences of nucleotides that are called microsatellites. They're like 1-6 nucleotide sequences that are repeated, like TATATA all in a row.
Erin Welsh	Mm-hmm.
Erin Allmann Updyke	So that's some basic definitions. Now on this podcast we talk a lot usually in the context of viruses or bacteria but this is true for human cells too, how every time our cells or any cell replicates it sometimes makes mistakes. And we call these mistakes mutations. Most of the time these mutations result in like a single or small base pair change, like one addition or a deletion or a substitution like a T for an A or something like that. But within these repeat regions, these microsatellite regions, a single mistake can lead to very big changes because what it often leads to is the gain or the loss of an entire repeat sequence.
Erin Welsh	Right.
Erin Allmann Updyke	So how does that happen? We don't fully know but we think that what happens is that as our DNA polymerase that's helping to replicate our DNA is chugging along copying TATATA all in a row, it kind of slips out of position and then it loses its place and when it picks it back up it does so earlier along that DNA chain. So if you have a region that's like TATA four times in a row and it gets a little bit wonky during replication, the next cell as after it replicates would end up with TATA like six times in a row or eight times in a row.
Erin Welsh	Mm-hmm.
Erin Allmann Updyke	So that's microsatellites. They exist throughout our genome and the mutation rate tends to be higher in these repeat regions than in other parts of our genome. And the longer a microsatellite region is, the more likely it is that this type of slippage and mutation can happen and the more likely that the mutation results in large changes especially expansion or growing of those regions and getting longer. So let's talk about how that relates to Huntington's disease.
Erin Welsh	Yeah.
Erin Allmann Updyke	Huntington's disease is a disorder that's known as a trinucleotide repeat disorder. So that means it's caused by an abnormal number of trinucleotide, three nucleotides in a row, C, A, and G that repeat a whole bunch of times, aka this is a microsatellite.
Erin Welsh	And there are other diseases that are this trinucleotide repeat diseases, right?

Erin Allmann Updyke	Absolutely, yes. So Fragile X is another example of a trinucleotide repeat disorder where you have a repeat at the end of the X chromosome. You also have Friedreich's ataxia, there's muscular dystrophy, there's a whole host of trinucleotide repeat disorders. This is one.
Erin Welsh	Mm-hmm.
Erin Allmann Updyke	And this happens in a gene that we all have on chromosome 4 that's called the Huntington gene where on chromosome 4 there's a series in everyone where we have this microsatellite, we have these CAG repeats but in the vast majority of the population, we have anywhere from 5 to like 28 copies of CAG all in a row.
Erin Welsh	Mm-hmm.
Erin Allmann Updyke	And another thing that's important about this repeat on chromosome 4 is that it's located in what's called an exon or a coding region, which means that our body, every human body and other animals too, we make a protein from this region that's called Huntington. It's a really clever name. But now we know that these microsatellite regions can sometimes be unstable and expand. And it turns out that once you get to above 28 repeats, that is when this region becomes unstable and that means that when those cells replicate, that particular region is likely to expand. It could contract but it's more likely to expand. And once it expands above 40 repeats, that is when a person will develop Huntington's disease.
Erin Welsh	Why 40? What happens at that point?
Erin Allmann Updyke	Okay, great question. So the 'why 40' is an interesting question because it could be a little bit earlier than 40, it really doesn't ever happen any earlier than 36 but especially that high 30 region you can have what's called incomplete penetrance where some people with that number of repeats might have disease and others might not. So that's kind of like a gray zone. But essentially the reason why once you have a certain number of repeats you end up with disease is because that trinucleotide repeat is located in an exon, in a coding region. So that abnormally long set of repeats causes the production of an abnormal huntingtin protein. And the more this repeat expands, the more abnormal this protein is. And probably the more abnormal protein you are producing as well.
Erin Welsh	Okay. So what does this protein do?
Erin Allmann Updyke	Okay, very good question. I'm not gonna answer this satisfactorily because the answer is normally we don't know. So we know that this huntingtin protein is essential to development because if you knock it out completely in mice, they don't live, like they don't develop in utero and they die. So we know that this protein does something that's very important, we think that it's involved with trafficking of stuff inside of the cell, like moving things from one place to another within the cell.
Erin Welsh	Within a cell, okay.
Erin Allmann Updyke	Within a cell. But we don't know that for sure. We don't know the real function of normal, typical, what they call wild-type huntingtin protein. But that still doesn't answer the question of how doe this actually cause disease? Like okay we have an abnormal protein, so what?
Erin Welsh	Yeah.

Erin Allmann Updyke	The short answer, I'm gonna try and give the shorter answer even though I think it's gonna be less satisfying, we don't really know.
Erin Welsh	(laughs) Erin, come on. That's not satisfying. Gimme the longer answer.
Erin Allmann Updyke	I know, I'm sorry. I warned you. We don't fully know. There's a lot of hypotheses about the specific cellular mechanisms that are involved with this abnormal protein, we have a lot of evidence that it's what's called a gain-of-function. So in for example our cystic fibrosis episode, we talked about how when you have a mutation in the cystic fibrosis protein, you lose the function of that protein and that's what causes disease. Here we have the opposite where the production of this abnormal protein is what's involved. It's not that the huntingtin protein is no longer doing whatever huntingtin protein is supposed to do, it's that it's doing something new and different and bad.
Erin Welsh	Right, right. Okay.
Erin Allmann Updyke	So we know that the accumulation of this abnormal protein, it forms aggregates, it forms these beta pleated sheets, they aggregate into cells, and then also possibly the mRNA itself that codes for this protein is somehow toxic to our cells and it causes cell death. So that's the end result is what happens is cells die because of this abnormal protein.
Erin Welsh	Mm-hmm.
Erin Allmann Updyke	And while huntingtin protein is found kind of throughout our body, like this gene is expressed in a lot of different tissues, for whatever reason this abnormal protein causes damage primarily to the central nervous system. So that's why we see this as a neurodegenerative disease because it's causing cell death in neurons.
Erin Welsh	Is it expressed more highly there or what? What's happening?
Erin Allmann Updyke	Good question. Don't fully know.
Erin Welsh	Okay.
Erin Allmann Updyke	At least I don't fully know. We can get even more specific and getting more specific will help us to understand the symptoms of Huntington's disease itself because we know the cells in our brain that are the most affected. One of the main areas that we see the loss of neurons and damage to neurons is in the striatum of the basal ganglia. So while we do see eventually the entire brain becoming involved and like widespread atrophy, this striatum of the basal ganglia is the first and hardest hit area. So what is the basal ganglia? We actually talked about this way back in our encephalitis lethargica episode a million years ago. Do you remember that?
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah, sure, okay.
Erin Welsh	No I don't, I don't remember.
Erin Allmann Updyke	Okay. Well let me tell you then. The basal ganglia, it's a set of brain structures that are deep in our forebrain that essentially help to control movement. So the basal ganglia helps to coordinate inputs from the motor cortex of our brain, they process them and then they put outputs out to the thalamus and other places that go to our muscles and actually initiate smooth muscle movement. Well, skeletal muscle, but I mean like smooth coordinated movement.

Erin Welsh	Okay. (laughs)
Erin Allmann Updyke	(laughs) It's also, the basal ganglia is involved in a lot of other things like cognition and emotion, like this is our brain, it's all very integrated. But one of the major functions is in this coordination of movement and a lot of what the basal ganglia does specifically is actually to inhibit movements.
Erin Welsh	Oh.
Erin Allmann Updyke	So that when this basal ganglia is damaged, we lose that ability to inhibit movement so movement becomes uncontrolled or uncoordinated.
Erin Welsh	Okay, and is this a common structure that is damaged in other movement disorders like Parkinson's or something?
Erin Allmann Updyke	Precisely.
Erin Welsh	Okay.
Erin Allmann Updyke	So in Parkinson's it's a different set of neurons and they're more specific and so that's why we actually have better treatments, we still don't have treatments to treat Parkinson's but to treat the symptoms we're better at Parkinson's than we are at Huntington's because of what is being damaged. But this region has more varied functions and so it's harder to target to fix.
Erin Welsh	Okay, gotcha.
Erin Allmann Updyke	Yeah. So that finally brings us to the symptoms of Huntington's disease. The characteristic symptoms which gave Huntington's disease an earlier name that I'm sure you'll talk about, Erin, the characteristic symptoms are chorea or choreiform movements. These are involuntary motor movements, especially in the extremities, so like arms and legs, fingers and toes. The involuntary movements, they're kind of like muscle twitches essentially that usually start out early in the course of disease in smaller muscles, so like fingers, face twitches, that especially early in disease might not be noticeable to anyone other than the person who's experiencing them, like you wouldn't even notice them. And they might not interfere very much at all with daily life. But eventually they spread to affect essentially any or every voluntary muscle which includes the muscles of the face and the throat that are involved in talking, chewing, swallowing. And so then dysarthria, which is difficulty speaking, can become a problem as well as dysphagia or difficulty swallowing and eating, which is very problematic.
Erin Welsh	Yeah.
Erin Allmann Updyke	And then eventually as this disease progresses, this increase that we see in muscle movement actually transitions to what's called hypokinesia and bradykinesia which means slowing of muscle movement and less muscle movement. And this causes like a difficulty in initiating voluntary movement. So muscles become very rigid and this is actually not unlike what we see in Parkinson's disease as well. You have a lot of rigidity in Parkinson's disease.
Erin Welsh	Right, yeah.

Erin Allmann Updyke	So of course all of these symptoms can have huge effects on a person's activities of daily living. Things like walking become very difficult and can result in frequent falls which can be very dangerous. But even activities like getting out of bed, showering, getting dressed, all of these can become difficult because you don't have control over the movements of your muscles. And then dysphagia, so difficulty swallowing, is particularly problematic because that can result in aspiration of food into the lungs which can result in pneumonia. But Huntington's disease is not just a motor disorder which is why the old name is no longer the name.
Erin Welsh	Right.
Erin Allmann Updyke	Huntington's causes a range of neurocognitive and psychiatric changes as well. So first, not first in terms of the course of disease but just first of what I'm gonna talk about, is depression which is far more common in people with Huntington's disease than in the general population. And I think what's important is that it might be easy if you just aren't thinking to dismiss this as the result of being diagnosed with an incurable, fatal disease. But it's not just that. Even though we don't fully understand depression in general and the effects of depression on the brain or every single change that happens in Huntington's disease in the brain, we do have a lot of evidence that the effects of Huntington's on the structure of the brain itself is what makes people more at risk for depression and other psychiatric illnesses like anxiety, psychosis, mania, etc.
Erin Welsh	Right, it's like actual physical changes.
Erin Allmann Updyke	Exactly, right. And then the other hallmark of Huntington's disease is dementia which is cognitive decline. So unlike Alzheimer's, so I think Parkinson's, Huntington's, and Alzheimer's often get talked about in relation to each other for different reasons but unlike Alzheimer's dementia which tends to affect memory first, especially short-term memory, the dementia and cognitive decline with Huntington's disease tends to affect what we call executive functions first, so that's things like decision making, planning, kind of like mental flexibility to new scenarios and reaction. And so this can result in behavioral changes and this is something that friends and family can sometimes notice, even sometimes before a person experiencing these changes might notice anything. But they can be very subtle and often can happen before any of these motor signs and can stay very mild for a long, long time throughout the course of disease.
Erin Welsh	Okay.
Erin Allmann Updyke	And this is likely because the basal ganglia is involved with a lot more than just motor coordination.
Erin Welsh	Right.
Erin Allmann Updyke	So these kind of small changes and small amounts of neuronal death scattered throughout can result in these changes. And because Huntington's does eventually affect the entire brain, eventually memory becomes impaired as well.
Erin Welsh	And so in terms of the progression and... First of all how predictable is it? Are there stages that you could say well this is the typical stage 1, stage 2, etc? And if it is predictable, why does that happen, why does it progress in that order?
Erin Allmann Updyke	Yeah, great question. There are stages in that there is presymptomatic and then what we call clinical disease which is after a person becomes symptomatic. And most of the time we consider symptomatic to be symptomatic with motor symptoms.
Erin Welsh	Okay.

Erin Allmann Updyke	But then a lot of times, you know, if you are talking with someone and they think about it, they're like, 'Yeah well maybe I have noticed a little bit of a personality change,' or 'I was having difficulties at work before that.' But they wouldn't have attributed it because they didn't know that they had Huntington's right, until the motor symptoms happened. But to answer your question, no, there isn't a sequence to this.
Erin Welsh	Okay.
Erin Allmann Updyke	And it can be very, very variable from person to person and the sequence does not depend on the number of repeats. So the vast majority of people with Huntington's disease will have onset some time between their 30s and 50s and everyone that has more than 40 of these CAG repeats will have symptoms by age 65 pretty much. But while the length of repeats doesn't correlate to what symptom is gonna be first or even how quickly the symptoms are gonna progress or anything like that, what it does correlate to is the early onset of symptoms.
Erin Welsh	Right.
Erin Allmann Updyke	So the longer this CAG repeat, the earlier you're likely to see symptoms onset.
Erin Welsh	And then that happens in successive generations, right?
Erin Allmann Updyke	Exactly, yeah. So something called anticipation happens where because this microsatellite region is so unstable with each generation that link is likely to become longer. It doesn't necessarily but essentially 75% of the time when that cell replicates, when any cell replicates that has that unstable repeat, it will expand. And so that means that a child with a longer repeat could have earlier onset of disease. Once you get to above like 60 repeats, you can have what's actually called juvenile onset Huntington's which happens if someone has symptoms before age 20. And that does tend to look a little bit different than Huntington's that has a normal onset of 30-50 where you have more of that slow, rigid movement early on in the disease rather than the choreiform involuntary movement. But what is kind of universal is that once symptoms begin, then the disease does progress and it continues to progress, it is essentially universally fatal within about 10-30 years of initial onset of symptoms. Most of the time, death is not from the disease itself but from complications associated with falls or more commonly with pneumonia due to aspiration because of that dysphagia and difficulty swallowing.
Erin Welsh	Mm-hmm, right. So we talk about this as a genetic, inheritable disease but can it occur randomly?
Erin Allmann Updyke	Yes. So it can certainly occur where there is no family history.
Erin Welsh	Right.
Erin Allmann Updyke	And that's because if you have a CAG repeat length of anywhere from like 26-35 or 28-35, that is an unstable length but you yourself and anyone in your family wouldn't have disease from that. But that microsatellite could mutate in your eggs or in your sperm and then your children could have Huntington's disease.
Erin Welsh	Gotcha, okay.
Erin Allmann Updyke	So we do see it happen, absolutely. I think I read, I should double check this number, but I think I read about 8% of the time.
Erin Welsh	Okay.

Erin Allmann Updyke	Yeah. So not super common but absolutely possible. So that's the biology of Huntington's disease.
Erin Welsh	I guess one question I didn't ask was why is it a later in life onset?
Erin Allmann Updyke	Yeah, it's a good question. It's likely related to that it takes that much time for this abnormal protein to accumulate. So remember that because this is an autosomal dominant disorder, you only need to have one copy of this gene so how often is your cell copying, making a protein based on that half, based on that mutated gene vs based on your normal copy? So like what's the ratio of normal huntingtin in your cells to abnormal huntingtin in your cells and how long does it then take to accumulate this toxic protein?
Erin Welsh	It's also interesting that there's not like a check system for abnormal proteins.
Erin Allmann Updyke	So it's very interesting and it's something that people are working on in terms of treatment. Like can we change how cells process protein and deal with it so that we don't have this accumulation of these abnormal protein sheets?
Erin Welsh	Right, yeah.
Erin Allmann Updyke	What I think is very interesting about the biology of Huntington's, Erin, is that we know so much, like I just gave you so much detail right? Like a lot of detail. And yet we also know so little at the same time.
Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	And I think a lot of that too has to do with just that we know so little about our brain, you know. Our brain is still... Neurocognitive disorders in general are not well understood. The mechanisms, the specific nitty gritties of it.
Erin Welsh	Right.
Erin Allmann Updyke	We just don't have the answers yet.
Erin Welsh	Well and then that of course like prohibits and good treatments form being developed quickly.
Erin Allmann Updyke	Exactly, yeah. So what I'm curious about Erin is how we got to this point. Like what is Huntington's like in history because it's been around forever, this protein is in us so how did we get to this point?
Erin Welsh	Yeah, yeah. I will try to answer those question right after this break.
TPWKY	(transition theme)
Erin Welsh	In the June 30th, 1806 edition of the Suffolk Gazette there's a brief news communication from East Hampton describing the tragic death of a woman named Phebe Hedges who was believed to have walked into the sea and not looked back. Quote: "This extraordinary step is attributed to her extreme dread of the disorder called St. Vitus' dance with which she began to be affected and which her mother now has to a great degree."

	This is one of the the earliest reports of what would later be described as Huntington's disease and I apologize for starting off in such a dark way but I think that there's a lot that we can tell from this really short description in this newspaper. First it shows us that St. Vitus' dance still seemed to be widely known. If you remember from our dancing plague episode, I'm gonna go over that briefly again later. Anyway the point is it was still widely known. Also that the disease can be extremely emotionally traumatic especially due to its familial nature like you talked about, Erin. And also that the exclusion or stigmatization of families where Huntington's was known to occur wasn't the rule, that in some communities like apparently in East Hampton, these families or individuals that had Huntington's were highly respected and very much integrated into and accommodated by the community.
	And I mention this last point because it serves as a sharp contrast for a good chunk of the social history of Huntington's and especially some of the prejudices that were created shortly after the disease was first described and that persisted long after that. So let's begin. Most histories of Huntington's disease start off with the man for whom the disease is named, George Huntington, but I wanted to go back a little further than that.
Erin Allmann Updyke	Of course you did, Erin.
Erin Welsh	Of course. Context, context, context. In case you haven't listened to our dancing plague episode which I think it's a pretty fun episode so I recommend it, right?
Erin Allmann Updyke	Yeah, definitely.
Erin Welsh	Essentially what happened was that in 1518, there were also other small outbreaks but the big one happened in 1518 in Strasbourg, there was this outbreak of contagious and unstoppable dancing. And sidenote, 1518 happened to be the year after a big sweating sickness outbreak in the area.
Erin Allmann Updyke	Ooh, it's all coming together.
Erin Welsh	All coming together. Okay. And so this dancing outbreak came to be called St. Vitus' dance or St. Vitus' chorea, 'chorea' from the Greek for dance, like choreography, etc. because people would go to the shrine of St. Vitus to be cured. And although the 1518 outbreak was the largest, it was not the only one and there were smaller outbreaks in the following years. and by the 1800s these epidemics had stopped happening pretty much entirely but the name of the condition or the condition itself didn't fade from public memory because other people still experienced these similar movement disorders like, for instance, Phebe Hedges who I just mentioned earlier. But what Phebe was experiencing in 1806 was not an outbreak of dancing plague of course, there was just no other name for it at the time. And St. Vitus' dance or just chorea was a sort of catchall term for any kind of movement disorder at that time. Really only starting in the 1800s is when clinicians started paying closer attention to these choreas, especially those that happened in children possibly because of the rise in rheumatic fever due to population growth, cities, growth, etc.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so when physicians started describing these cases, they may have also noticed another kind of chorea, one that was different from this childhood or Sydenham's chorea. By the time that George Huntington's description of the disease was published in 1872, there were at least five other previous descriptions of the disease going back to like the 1840s.
Erin Allmann Updyke	Huh, interesting.

Erin Welsh	But we call it Huntington's, not Water's disease or Lund's disease.
Erin Allmann Updyke	Why?
Erin Welsh	Yeah, well it might just be a matter of timing and visibility and chance.
Erin Allmann Updyke	Okay.
Erin Welsh	But another thing that made Huntington's stand out was his description which the famous doctor William Osler said, quote: "There are few instances in the history of medicine in which a disease has been more accurately, more graphically, or more briefly described." So.
Erin Allmann Updyke	Huh. So just like a very, very good description.
Erin Welsh	Yeah.
Erin Allmann Updyke	So he won the best description award.
Erin Welsh	He won the best description award.
Erin Allmann Updyke	Okay.
Erin Welsh	And at the tail end of Huntington's publication which largely focused on other forms of chorea, Huntington's added a few paragraphs on what he called hereditary chorea. Noting its inherited nature, particularly that it didn't skip a generation, mental decline as a common occurrence, and it's typically adult onset. It was descriptive yet to the point and in the decade after it was published, the disease that would later be called Huntington's chorea for this amazing description would get a whole lot more researchers interested in it and not always for good reason. But before we get to that I wanna talk a bit about why the disease might have only been described in the late 1800s which seems kind of late to me.
Erin Allmann Updyke	Yeah.
Erin Welsh	Like you know, St. Vitus' dance had been around for a long time.
Erin Allmann Updyke	That's like 300 years between...
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so it might just be that like here are accounts that people can't distinguish between St. Vitus' dance and what might have been Huntington's, I'm not sure. But one of the things that people have suggested Is that low life expectancy may have contributed to the apparent invisibility of the disease.
Erin Allmann Updyke	Yeah.
Erin Welsh	So people were more likely to die of something else before developing any symptoms.

Erin Allmann Updyke	Right, that makes sense.
Erin Welsh	Yeah, which would also then sort of obscure the inheritability aspect of it.
Erin Allmann Updyke	Right.
Erin Welsh	But having said that, it's not like the 1800s, it's not like the year from 1799-1800 came with this huge boost in life expectancy.
Erin Allmann Updyke	(laughs)
Erin Welsh	For example, if you were born in 1601, your life expectancy was 38 years.
Erin Allmann Updyke	Oh no.
Erin Welsh	Whereas if you were born in 1831, life expectancy was 41 years.
Erin Allmann Updyke	Okay.
Erin Welsh	Like from birth.
Erin Allmann Updyke	Wow.
Erin Welsh	And there are problems with life expectancy from birth because infant mortality was so high, etc.
Erin Allmann Updyke	Right.
Erin Welsh	But anyway. So other people argue that it actually wasn't this slight increase in life expectancy but rather the reframing of heredity overall and how we thought about the inheritance of traits.
Erin Allmann Updyke	What?
Erin Welsh	Yeah. So there was this boom around this time in natural history research and experimentation and livestock and plant breeding that had led to people thinking critically and publishing widely about the inheritability of traits.
Erin Allmann Updyke	Like Mendel.
Erin Welsh	Like Mendel, like Darwin, like if you remember back to our prions episode, like all of the people who were doing sheep breeding at that time to try to find the best merino wool.
Erin Allmann Updyke	Yeah. Right, yeah.
Erin Welsh	And also in medicine there was still no germ theory in the early 1800s and so heredity joined miasma as this way to explain why certain diseases occurred.

Erin Allmann Updyke	Right.
Erin Welsh	So there's that. And finally there's the matter of George Huntington and East Hampton. So the man and the place. George's grandfather Abel who was also a doctor moved to this area of Long Island, New York in the late 1700s where he set up a medical practice. And shortly after he arrived, he learned of a few families in the area who were affected by something that people generally referred to as quote "that disease".
Erin Allmann Updyke	Oh.
Erin Welsh	The people who had that disease and their unaffected family members were not shunned or stigmatized. They held public office, they seemed to be supported by their families and by the rest of the community, it was just sort of like the way that it is, it was like, 'This is how we are here'. And George's father also became a doctor and some of his patients were also people with what would later be called Huntington's disease and sometimes George would go on rounds with his dad. And so when George finished medical training, he not only was equipped with the ability to observe and describe certain conditions, he had the generational knowledge of his father and grandfather and he also happened to live in a town which had a higher prevalence than in surrounding areas.
Erin Allmann Updyke	Okay.
Erin Welsh	And so this set him up to write his 'On Chorea' in 1872. It was the only article he ever published, apparently.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah. When his paper came out, other reports of Huntington's started to trickle in and not just from the U.S. Germany, France, Italy, Britain, Austria, Cuba, Poland, Russia, and many other places reported case descriptions of what had started in 1887 to be called Huntington's chorea. And this research in the late 1800s filled in the details of the clinical picture that Huntington had painted. So for instance, insanity was mentioned as a defining feature in George Huntington's description of the disease but later physicians noted that the mental impairment due to the disorder was not always severe or it was variable or it onset differently and it was essentially their understanding or how cognitive function worked became more nuanced.
Erin Allmann Updyke	Yeah, yeah.
Erin Welsh	And then the average age of onset was studied. Autopsies were performed on people who had died from Huntington's and these showed these physical changes in the brain. And there was a whole lot of compare and contrast with the other highly studied form of chorea from this time, so Sydenham's chorea. William Osler, who was super interested in all types of chorea, got in touch with Huntington to ask whether he could arrange a meeting with some people who were affected by the disease in the town and Huntington said, 'No, I don't think that's a good idea, I want to respect these people's privacy and you shouldn't bother them.'
Erin Allmann Updyke	Wow.
Erin Welsh	Which like in the late 1800s I'm shocked by.
Erin Allmann Updyke	I'm totally shocked.

Erin Welsh

I know.

Erin Allmann Updyke

Way to go.

Erin Welsh

Yeah.

Erin Allmann Updyke

I'm guessing Osler didn't listen?

Erin Welsh

Actually he did, yeah.

Erin Allmann Updyke

Okay.

Erin Welsh

He was like, 'Okay.' And then Huntington moved away to a different town and another doctor took over the practice and Osler asked him. And at first this new doctor, Osborn, said the same thing that Huntington had said. 'No, it's best if you don't come here.' But then he changed his mind and it seems that he thought that maybe by having Osler come there to do more research on the disease it could increase awareness that could lead to more support and medical treatment and cures. But on the other hand it could bring increased scrutiny and unwanted attention to these people without their consent. Osler never did end up visiting East Hampton, he did conduct research on Huntington's disease on other families in other places. But in the last few years of the 19th century and in the first several decades of the 20th, Huntington's and Osborn's initial fears were realized as the focus on Huntington's turned to one of the defining characteristics of the disease, its heritability.

So like I mentioned, general patterns of inheritance had been figured out for a while by the end of the 1800s thanks to livestock breeders who really could be considered like the first geneticists, even more so I would argue than Mendel. By the time Mendel was playing with his peas in the 1860s, these breeders already knew about dominant and recessive forms of inheritance. Maybe not in that formal language but they were incredibly knowledgeable. But interest in the field of heritability grew throughout the late 1800s and into the 1900s, especially when Mendel's work which was published in 1866 but was sort of lost, like no one talked about it and it was rediscovered in 1900. Yeah. And Mendel's work gave this form and calculation and structure to these patterns. And the interest grew even more broadly beyond that. It wasn't just plant of livestock breeders or natural historians that had an interest in which traits were passed down, but also so-called "social thinkers", quote unquote, who began to take these biological concepts and apply them to what they saw as social problems. So begins the story of eugenics.

And this is a story that I've touched on so many times in this podcast. If you remember back in any of the episodes where I talk about eugenics, especially I think the birth control episode, you may remember how the term "race suicide', quote unquote, really gained traction in the early 20th century in the U.S. It was one of Teddy Roosevelt's favorite terms. Basically white middle class Americans began to be fearful of the influx of immigrants, the growth of the lower class, their own declining birth rate, etc. Essentially they were worried that they were going to become outnumbered by those they deemed to be unfit or less than. The word 'degeneration' itself began to take on multiple meanings. It could be used medically to describe how someone's ability to walk and talk and function normally slowly deteriorated and to the eugenicists it can be used to vaguely describe the gradual decline of society, whatever that meant. However they wanted it to mean.

	Eugenics and this concept of race suicide focused particularly on who was procreating and how to control it. They wanted to encourage certain people to procreate more and prevent others from procreating at all, by force if necessary. The first few decades of the 20th century saw the rise of eugenics from this niche theoretical biology concept to a widespread public movement with state laws legitimizing this way of thinking and genetic research providing a scientific basis for it. Marriage prohibition, involuntary sterilization, racist immigration laws, those were all like the order of the day. And I think I'm probably repeating myself from past episodes when I say that Hitler and the Nazi Party got many of their ideas directly from the eugenics movement in the United States. It's hard to overstate just how pervasive eugenics became and in some ways still is today.
	Anyway, as eugenics gained traction it began to hone in on certain groups of people or individual traits or conditions that they felt were, quote, "unfit". One of these was Huntington's disease. Huntington's disease was actually one of the first genetic diseases to be described as dominant by William Bateson and Reginald Punnett, of like Punnett Square fame.
Erin Allmann Updyke	Whoa.
Erin Welsh	In 1907. And you know this is something that I think I have to relearn every so often but just as the 20th century birth control movement in the U.S. has its roots in eugenics, so does the study of genetics.
Erin Allmann Updyke	Yeah, I always have to relearn that as well.
Erin Welsh	If someone was a geneticist in the early 1900s, they were very likely also a eugenicist. Since George Huntington first described the condition in 1872, there had been no substantial developments in terms of treatment of the disease and because of this eugenicists then increasingly turned towards emphasizing prevention, either through sterilization, restricting immigration, or outlawing marriage. Enter Charles Davenport. Charles Davenport may not have started the eugenics movement in the U.S. but he was friends with Francis Galton who was the father of eugenics and he also founded the Eugenics Record Office in 1910 where field workers and scientists were trained in how to collect and analyze data to push their eugenic propaganda. Osborn's fears about the increased attention to the residents of East Hampton and elsewhere with Huntington's disease were about to come true.
	After Davenport read about the genetic basis of Huntington's and its patterns of inheritance, he viewed it as a perfect subject for a large-scale project in which he would identify the source of the disease in the U.S. as well as shed more light generally on heritable disease. The person responsible for carrying out much of this study was the eugenics field worker, which like I can't believe is an actual phrase, a job title. Eugenics field worker.
Erin Allmann Updyke	Yeah. In the 1900s.

Erin Welsh	Yes, yeah. Named Elizabeth Muncie. Muncie would go around to towns in different states where families with Huntington's had been identified, both to interview them as well as construct a family tree. Over her years as a field worker she created pedigrees with over 5000 people and identified nearly 1000 people with Huntington's, about 250 of which were still living at the time of her survey. And while I was reading about this I just could not stop thinking about how horrifying it is that there was a Eugenics Record Office collecting the names and locations of people with certain diseases. And we can get a taste as to what could have happened with this info in the U.S. hypothetically by looking at what did happen in Germany. In the years leading up to WWII, people with Huntington's were among the hundreds of thousands of people forcibly sterilized in Germany. Of the 350,000-400,000 people sterilized in Germany during 1933-1939, around 3000-3500 of those people were people that had Huntington's. And then when the war started, so did the exterminations and we don't really have good numbers for that with regards to people with Huntington's.
	Anyway, back to Muncie and her field work. Rather inconveniently for Charles Davenport who held these prejudicial views that people with diseases of any kind were degenerate or feeble-minded, Muncie actually gained a great deal of admiration and respect for many of the people that she interviewed. I mean she was still a eugenicist, let's not forget that.
Erin Allmann Updyke	Yeah.
Erin Welsh	But what she found was that there was no hard and fast rule as to who developed chorea and who didn't in terms of like, 'Oh this person is a scoundrel. Oh this person is really well respected in the community.'
Erin Allmann Updyke	Right, it has nothing to do with who you are or what you do for a job or anything like that. Yeah.
Erin Welsh	Mm-hmm. And this went against the prevailing thought of the day, at least for the eugenicists, that the disease was specific to lower classes. And that was a notion that persisted well into the 1960s in terms of Huntington's. Charles Davenport and Elizabeth Muncie published the data that Muncie collected in 1916 in the - get this, this is an actual journal - American Journal of Insanity.
Erin Allmann Updyke	What?
Erin Welsh	Yes. I wonder when it stopped being a journal or what it turned into.
Erin Allmann Updyke	I know, it probably just turned into something. Can we google that?
Erin Welsh	I'm googling it. It lasted until 1921 I think. Oh, American Journal of Psychiatry, I'm pretty sure.
Erin Allmann Updyke	Bah-bah-bah.

Erin Welsh	Yeah. So what they showed in this article was a much more varied picture than the one that George Huntington had painted nearly 40 years prior. In it they discussed the variability of the disease, both in symptom severity and age of onset. In general though the paper was terrible statistically and broad claims were made about the unfitness of these families and the bad characters at the top of the family tree. This article was essentially used as this platform for his eugenic propaganda. And this way of thinking about Huntington's didn't die out with Davenport, unfortunately. If anything this article and that research, quote unquote "research" added fuel to the fire. Based in part on Davenport and Muncie's publication, there's a Connecticut psychiatrist named Percy Vessie who created an origin story of Huntington's in the U.S. as one in which witchcraft and scoundrels featured prominently from the very beginning.
Erin Allmann Updyke	Oh come on.
Erin Welsh	I mean this account was based on horrible research and just an absence of facts. Everyone in his story was either described as a criminal or a lowlife of some kind and he smeared the name of every person he listed. He then blamed Huntington's disease for their behavior. And in 1932, he used this article to urge sterilization. His fiction of witchcraft and criminality associated with the disease was thoroughly, entirely, completely disproven but only in the 1960s.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah so it was repeated and repeated and repeated and still I saw it in some papers from like the 80s.
Erin Allmann Updyke	Oh no.
Erin Welsh	Yeah. This story, which also I will note has been reclaimed by some people with Huntington's as a way to sort of show the enormous prejudice and exclusion faced by people with he disease and the difficulties in overcoming that.
Erin Allmann Updyke	Yeah.
Erin Welsh	But this story created the set of stigmatizing associations that persisted in Huntington's literature for decades. I was shocked but also not shocked to find out that in 1951 there was an article published in the Journal of Science, like this extremely prestigious journal, in which the authors claimed that there was enormously higher fertility in men with Huntington's compared to their siblings that did not have the disease. They used a sample size of two. Two brothers, that's it.
Erin Allmann Updyke	What?
Erin Welsh	1951 science magazine.
Erin Allmann Updyke	Science.
Erin Welsh	These claims were refuted 8 years later. 8 years later.
Erin Allmann Updyke	8 years?
Erin Welsh	Yeah. After WWII, the U.S.' Infatuation with eugenics was mostly over and research on Huntington's turned towards treatment and molecular diagnosis. And I just wanna say that I feel like I spent a lot of time on eugenics and I do all the time in these episodes.

Erin Allmann Updyke	Yeah, it's like every other episode I think these days we're talking about it.
Erin Welsh	Yeah it's a horrible and depressing topic. But I feel like it's not talked enough about in history or biology classes, at least in the ones that I took, maybe that's different now.
Erin Allmann Updyke	Yeah.
Erin Welsh	But I think it's really important to remember how people can misuse or misquote or straight up make up information to push their own propaganda, by couching something in science or scientific language, you can really cause a lot of harm if your claims are not supported or if you're pushing some sort of propaganda.
Erin Allmann Updyke	Right.
Erin Welsh	And I think in the U.S. we have this tendency to ignore the dark part of our history and pretend like we were the heroes, we were the saviors in like all of our stories.
Erin Allmann Updyke	Right. Yep.
Erin Welsh	We have to acknowledge our past, our dark past, so that we can be better.
Erin Allmann Updyke	Yeah.
Erin Welsh	It has to happen. I think also a lot of the response that some people have about eugenics is like, 'Oh well it was another time. You have to understand it in the context of that time.' And it's like you can both understand why eugenics became popular in the context of the time and also be horrified that it became popular and that state laws existed.
Erin Allmann Updyke	Exactly. Yeah.
Erin Welsh	Like those two things are not mutually exclusive.
Erin Allmann Updyke	In fact they are both true. (laughs)
Erin Welsh	Right, it's just like this happened to people. This actually did happen to people. How do we not have this happen again?
Erin Allmann Updyke	Yeah.
Erin Welsh	Let's just be better.
Erin Allmann Updyke	Let's try.
Erin Welsh	Anyway, speaking of better and better things, along with the renewed scientific interest in Huntington's, there was also the birth of several advocacy and support programs. The first was the Committee to Combat Huntington's Disease, now called the Huntington's Disease Society of America founded by Marjorie Guthrie in 1967. The same year that her husband - and this is what cracks me up, Erin, cause every time I said this to you you were like, 'I don't know who that is. I don't know who that is.'

Erin Allmann Updyke	So I feel like you were talking about him in a completely different context recently and I was like yeah, I don't know who that is. And I didn't even realize that it was Huntington's.
Erin Welsh	Yeah. Woody Guthrie.
Erin Allmann Updyke	Yeah, Woody Guthrie. I didn't know who that was. And then when I saw his name on the Wikipedia page I was like, oh! I know who he is now!
Erin Welsh	That's the guy that Erin keeps talking about. (laughs)
Erin Allmann Updyke	Yeah. I thought you were just talking about him for other randoms reasons. He's like music, right?
Erin Welsh	(laughs) He's like music, yeah.
Erin Allmann Updyke	Listen.
Erin Welsh	Woody Guthrie was an incredibly influential folk singer/songwriter, so he inspired like the whole folk music generation. He wrote The Land is Your Land for instance.
Erin Allmann Updyke	Oh, I know that song.
Erin Welsh	Lot of other songs that you would recognize, his guitar said "This machine kills fascists" which is also another thing I was thinking for our quarantini name.
Erin Allmann Updyke	(laughs) Ooh, that would be good.
Erin Welsh	Anyway, so Woody Guthrie started to develop symptoms of Huntington's in the 1940s and finally was diagnosed in 1952.
Erin Allmann Updyke	Okay.
Erin Welsh	And Marjorie, when he got his diagnosis, she is asking the doctors all these questions and the doctors were just like, 'Well that's it, sorry. There's nothing we can do, there's no advice I can give you, that's it.' And she was like, 'No, I'm not going to accept that. This isn't it. I want to talk to other people who've experienced this, I want to bring us all together so that we can get support, so we can get advice, so we can raise awareness to get more information about this disease.' And so in 1967, which was the same year that Woody Guthrie died of the disease, she founded this organization where other people could find information and get support. And this organization, her mission was instrumental in shedding light on this disease, getting people to talk about their experiences, and how the medical establishment was frankly failing them. And later on in navigating the very complicated issues of testing, insurance, financials, genetic counseling.
	Because of all of these years of prejudice surrounding Huntington's and stigma and shame, there was sort of this culture of almost like silence around the disease. So like even within families, it wasn't necessarily acknowledged and I think that in more recent years due in large part to this organization and other organizations that were founded, there's been a push to increase awareness and to stop talking about it in these eggshell tiptoe terms.

Erin Allmann Updyke	Right, like hushed tones.
Erin Welsh	Like let's talk frankly about this disease and what we can do about it and what are the different options, what is the research telling us, what support can be provided.
Erin Allmann Updyke	Yeah.
Erin Welsh	And on the other side of things there was another organization that was founded more on the scientific angle, on the scientific research angle called the Hereditary Disease Foundation started by Dr. Milton Wexler whose wife Leonore died of Huntington's. Also two of their daughters, one named Alice is a historian I believe and she wrote one of the books I read.
Erin Allmann Updyke	Oh wow.
Erin Welsh	And another of their daughters named Nancy is a geneticist that helped to do like a ton of Huntington's disease research. So very cool.
Erin Allmann Updyke	Wow. That's very cool.
Erin Welsh	So this foundation had a different aim, they wanted to understand the mechanism of the disease. So in the early 1960s, researchers came across a large cluster of people with Huntington's disease in the Zulia region of Venezuela by the shores of Lake Maracaibo. In this group of people, Huntington's was at a particularly high prevalence, so there were even some people suspected of being homozygous for the trait, meaning they had two copies of the mutated allele. And this group of people was studied by the foundation and ultimately, just to sort of long story short it, in 1983 a marker for the gene was found and its location was identified as being on the fourth chromosome.
	And ten years later in 1993, the last big point in the timeline of Huntington's disease so far, the exact gene was found. And isolating the gene for Huntington's disease was huge. On the scientific front it allowed for researchers to understand how this allele produced the effects that it did and to try to come up with potential therapies. And from the patient's point of view, it held answers because identifying this gene meant that you could be tested for the disease. But it's not as simple of that of course.
Erin Allmann Updyke	Yeah.
Erin Welsh	Because with this new ability to test came a bag of ethical considerations since this was a heritable disease. So for instance, if a parent did not want to get tested but you did and you found out that you were positive, how do you deal with that? And Erin, I know you're gonna talk a bit more about this aspect so I'm just gonna kinda wrap it up here and say that we've come a long way in our understanding of Huntington's disease and how it works and in reducing some of the stigma and shame that used to be so prevalent. But just like you said, in many ways we are kind of right where we were at the beginning.
Erin Allmann Updyke	Yeah.
Erin Welsh	So Erin, I'm hoping that you'll tell me the ways that we've gotten better and maybe some hope for the future?
Erin Allmann Updyke	I'll try to. We'll take a quick break first.

TPWKY	(transition theme)
Erin Allmann Updyke	So before we talk a little more about the genetic testing bit, let's just quickly go over the numbers. Overall, the prevalence of Huntington's worldwide on average is somewhere between 4 and 10 per 100,000 people.
Erin Welsh	Okay.
Erin Allmann Updyke	It does vary quite a bit based on region and we don't fully know why, like why this region is more prevalent than others. But in general in Asia the prevalence tends to be far lower, that's where it's kind of the lowest worldwide, it's estimated there at about 0.5 per 100,000 people. In Western, Central, and Eastern Europe, so all over Europe as well as the U.K. prevalence estimates have varied between 2 and 7 per 100,000. In Africa where we don't have as good of estimates, they've varied between 1 and 4 per 100,000. In Oceania it's estimated at 5 per 100,000 and then in North America 7 per 100,000. But this also varies a lot within North America.
Erin Welsh	Okay.
Erin Allmann Updyke	South America, outside of that region in Venezuela that you mentioned which is much higher, we really don't have good numbers on the rest of South America, very limited data. But so worldwide overall, like 5-10 per 100,000 people. And like I said in the biology section, the mean age of onset is around 40 years, so 30-50 years and then life expectancy tends to be about 10-20, maybe 30 years once symptoms appear.
Erin Welsh	Okay.
Erin Allmann Updyke	And that part doesn't vary based on income, based on country, based on anything. And that's largely because even though individual manifestations of this disease can vary, like the overall course doesn't really vary and the way that we deal with it in all these different countries regardless of the country's income doesn't really vary either. So to kind of get into both what we can do for treatment and then also what you were mentioning, Erin, about this ethical dilemmas when it comes to genetic testing. The bottom line is that right now in terms of treatment, we have nothing that can change the course of disease. We don't have any medicines or treatments that can address the underlying issues or the progression of disease. We have symptomatic treatments, especially for the choreiform movements, those involuntary motor movements, we have drugs that affect dopamine pathways and some other things that can help with those involuntary movements.
	We also have drugs that can treat things like depression and anxiety, antipsychotics if psychotic symptoms develop. So we have those kind of psychiatric drugs but we don't have anything specific to Huntington's and we don't have anything to address the underlying issue itself. And so in part because of that this is not a genetic disorder like, for example, cystic fibrosis or sickle cell disease that we've talked about before where early identification can lead to vastly improved outcomes because of the treatment options that we have available, right. This is not that. And so genetic testing can tell a person that they have this gene and can tell them that they are going to develop Huntington's or not but it has sparked quite a lot of debate about when and whether to do genetic testing especially when it comes to children. Like at what age should someone be allowed to decide that they want to get tested?
Erin Welsh	Yeah.

Erin Allmann Updyke	But it also brings up ethics in regards to the idea that of course ethically everyone has a right to know their own health status, right. I have a right to know what's going on in my body. If there's a test that can tell me that I have a genetic disorder and I want to know it, I have a right to know that. But every person also has a right to not know and I have a right to keep all of my information secret to me if that's what I want.
Erin Welsh	Yeah.
Erin Allmann Updyke	So like you mentioned, Erin, a person getting genetic testing done for something like Huntington's that is autosomal dominant necessarily discloses information about the parents' health status.
Erin Welsh	Right.
Erin Allmann Updyke	That they may or may not have wanted disclosed. It also could release information about for example, an identical twin.
Erin Welsh	Oh yes.
Erin Allmann Updyke	Right? And so there is a lot of kind of ethical issues surrounding this.
Erin Welsh	So regarding all these like ethical considerations and whatnot, do you know how much that happens to vary country to country?
Erin Allmann Updyke	Very good question. I do not. I imagine it could vary quite a lot, especially because when it comes to disease and how much people want to know, culturally that varies hugely in different countries. So in some places, like people don't want to know necessarily especially if the outcome is going to be bad, right.
Erin Welsh	Right.
Erin Allmann Updyke	And so I imagine that it varies quite a lot.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah. So there's not an answer to this, right. It's very person-specific and so this is the kind of thing that really has to be a discussion between an individual and their healthcare provider.
Erin Welsh	Mm-hmm, yes.
Erin Allmann Updyke	And genetic counselors especially. But Erin, I like to try to end these episodes on more hopeful notes so let's talk about the future.
Erin Welsh	Gene therapy.
Erin Allmann Updyke	Gene therapy. And really I think that one of the things about how much we do know about Huntington's is that even if we don't know every detail about the specific mechanisms, we know a lot and we know enough to know that gene therapy is a real possibility for treatment of this disease.
Erin Welsh	Yeah.

Erin Allmann Updyke	And that's I think really, really incredible. So there are a lot of different possibilities and there are people working on kind of all of these different... I have links to a number of papers that go in a lot of detail on all of the different research that's being done and the different kind of ways that you could target Huntington's disease from a variety of different angles with gene therapy.
Erin Welsh	Okay.
Erin Allmann Updyke	So a lot of it is maybe using something like RNAi which are little small pieces of RNA that can go in and kind of make changes. I think that the most exciting prospect is CRISPR-
Erin Welsh	Oh yeah.
Erin Allmann Updyke	Which we talked about in a lot more detail in the sickle cell episode because there I think we're a little bit further along than we are in Huntington's. But CRISPR, just for anyone who hasn't listened to that or who has forgotten, is a way by which you can go into a cell and make very specific targeted changes one time that persist for the life of that cell. So you can actually change the DNA very specifically and cut out that mutant Huntington's gene and replace it with a non-mutated, like a normal type Huntington's gene. And you can do so with one treatment whereas most gene therapies that are in development would require a lot of infusions, which is especially difficult for neurodegenerative diseases where you have to be able to get that into the brain, so that requires like going directly into the brain which is very problematic or very difficult.
Erin Welsh	Yeah, that sounds very risky.
Erin Allmann Updyke	Yeah. But there are a number of different strategies, some gene therapies might try to reduce the expression of this mutant protein, so you might still make some of it but you just wouldn't accumulate those toxic levels because you're making less of it.
Erin Welsh	Okay.
Erin Allmann Updyke	Others like I mentioned, especially CRISPR, would just cut that mutated region out and replace it with a normal region. And then there are other therapies that are being developed aside from just gene therapy to try and address the downstream effects as well, like try and improve cognitive decline by addressing things like mitochondrial function which we think is very involved in dementia and cognitive decline in general.
Erin Welsh	Huh, okay.
Erin Allmann Updyke	So there is a lot of research being done. If you look at clinicaltrials.gov and you search for Huntington's, you can find over 1500 studies that are being done. Not all of those are drug studies or treatment studies but that is a lot, it's like on par with cystic fibrosis and things like that when you kind of just search for those studies.
Erin Welsh	Okay.
Erin Allmann Updyke	I'll link to a website where you can check specifically gene therapy studies. There are six studies currently listed on the gene therapy clinical trial database. Some of them are stem cell studies cause that's another possibility is using stem cells to just like regrow the brain tissue that is damaged.
Erin Welsh	Whoa.

Erin Allmann Updyke	That's like a whole other mechanism. And some of those kind of address dementia in general, not just only Huntington's. But there are at least two gene therapy studies specifically that are in phase 1 and phase 2 trials, so human trials for kind of safety and feasibility.
Erin Welsh	That's cool.
Erin Allmann Updyke	Yeah so it is on the horizon. And I'll also link to another nature, just sort of write up article, not like a peer-reviewed publication, but an article about a group that's working on CRISPR specifically for Huntington's.
Erin Welsh	Cool.
Erin Allmann Updyke	So like there's a lot of hope, I think. And there's a lot on the horizon that could potentially come to fruition. How quickly how many people currently living with Huntington's will be able to see those benefits, I don't know. But I believe it's possible.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. So that's Huntington's.
Erin Welsh	Wow, that was a big one.
Erin Allmann Updyke	It was, yeah. So sources?
Erin Welsh	Sources! I wanna shoutout just a couple in particular, I have a bunch but I wanna shout out by Alice Wexler, 'The Woman Who Walked into the Sea'. And also a textbook by Bates, Harper, and Jones called 'Huntington's Disease', those had great history sections. And then I have a bunch of other additional papers.
Erin Allmann Updyke	I also have a number of papers, especially interesting I think are the ones looking at the future, like targets for future clinical trials in Huntington's disease and the slowing of neurodegeneration in Parkinson's disease and Huntington's disease, future therapeutic perspectives. You can find the list of all of our sources from every single episode on our website thispodcastwillkillyou.com under the EPISODES tab.
Erin Welsh	Thank you again so much to Jay for providing their firsthand account for this episode, we really, really appreciate it.
Erin Allmann Updyke	Yeah, we do. Thank you. Thank you also to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Welsh	And thank you to the Exactly Right network of whom we are a very proud member.
Erin Allmann Updyke	And thank you to you, listeners, we really appreciate you listening to this podcast, we really like making it even when it's a tough topic to talk about.
Erin Welsh	Yeah. We really do and we appreciate you sticking with us all this time.
Erin Allmann Updyke	All this time.

Erin Welsh	Letting us make this podcast, essentially.
Erin Allmann Updyke	Yeah.
Erin Welsh	Well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals.