0:04
Hello, everyone, welcome. We're here to listen to a very interesting topic this afternoon, hereditary neuropathy and genetic taste testing, presented by the Foundation for Peripheral neuropathy and kindly sponsored for us by El Nylon Pharmaceutical.

0:25
Want to introduce myself, my name is Nancy Froman. I'm the Director of Development and Marketing for the Foundation for Peripheral Neuropathy, and here with me on my colleagues as well, Tanya and Lindsay.

0:39
We will be your host for this afternoon.

0:44
Before we begin, just a couple of housekeeping notes. This presentation will be recorded. We will send you a recording link by e-mail, so you can view it later. We'll also have the recording up on our website in the next few days.

1:02
If you have questions for our experts, we will be addressing as many of them as we can at the end of this session. Please put your questions in the question box.

1:13
And we will, we will see them, and we will try to answer them. You, if we can't get to them during this session, we'll try to get to them in another point in time. And if you're having trouble with the audio, you can dial in by phone. There'll be a number in the e-mail that was sent to you with registration information.

1:38
Aye.

1:39
Like two, start off, and go, Doug, jump right in and introduce our two speakers who have come to us this afternoon to share their expertise and their knowledge with us.

1:51
The first is doctor Brett McCray.

1:55
Doctor McCray is an Assistant Professor of Neurology at Johns Hopkins. He is a physician scientist with a clinical and research focus on Charcot Marie Tooth, CMT Disease, and other forms of peripheral neuropathy. He currently serves as the co-director of the Johns Hopkins CMT Clinic, and the Johns Hopkins Site Principal Investigator for the Inherited Neuropathy Consortium.

2:22
Genetics and natural history CMT study, in addition to caring for patients, he also runs a basic science lab, focused on the pathogen, genesis of inherited forms of peripheral neuropathy.

2:36
His current work is focused on understanding the pathogenesis of CMT type to see. And he's establishing a registry for patients that fall into this subset of patients. And, after doctor McCray, we will have Cristi Smith joining us, who is a Board Certified Genetic Counselor at Johns

Hopkins Department of Genetic Medicine. She sees pediatric and adult patients with a special interest in those with inherited forms of neurology, neuro muscular disease, retinal disorders, and pediatric cancers.

3:11
She received her Masters of Science and Genetic Counseling from Johns Hopkins National Human Genome Research Institute.

3:20
In addition to our clinical work, she's an active member of the National Society of Genetic Counselors, Maryland, DC Society of Genetic Counselors, as well as a member of the American Board of ...

3:32
genetic Counseling, and she teaches with addition to all of those other activities. We thank them for joining us today and without further ado, I welcome doctor McCray to start us off on inherited and Hereditary neuropathy.

3:49
Thanks, Nancy. Thanks for the nice introduction and for the opportunity to speak to this group today.

3:54
So I'll jump right in since Nancy did such a nice job of introducing me, um, control here.

4:04
So first I want to just give you sort of a perspective or neurologist perspective on how we think of peripheral neuropathy.

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And this may be something many of you know, but hopefully, it can give you a little bit of a sense how we think about Iraq.

4:16
So we sort of think of the nervous system in terms of the brain and spinal cord as the central nervous system.

4:22
And then the things beyond that, that leave the spinal cord makeup, the peripheral nervous system.

4:28
And so when we talk about peripheral neuropathy, we're really talking about these nerves after they've left, the brain and spinal cord entered into the periphery of the body.

4:38
So if you have a sensory neuropathy, this is an RFA that affects the sensory nerves. This can lead to a number of different symptoms is, in, many of you may know, can cause numbness or sort of lack of sensation, or can cause extra, abnormal sensations, which can range from tingling to pain to other sort of strange or unusual sensations that it can be really hard to describe, electrical, sensations, pain, cold, etcetera.

5:04

Then neuropathy can also affect the motor nerves. And when that happens, they affect strength, and can also lead to reduction in the bulk of muscles, what we call muscle atrophy.

5:15
So peripheral neuropathy in general usually follows a pretty typical pattern.

5:20
And so one of the main features is that it's usually symmetrical, meaning that it affects both sides of the body equally.

5:27
So if you have neuropathy in your feet, usually the feet feel about the same, and same in the hands. Usually, there's not big differences between either side of the body.

5:36
And the other thing that we think about a lot is what we call the length dependent nature of peripheral neuropathy.

5:42
And so what this refers to is that in most forms of peripheral neuropathy, whether they're inherited or not, they affect the longest nerves first, and those longest nerves go to the feet, and toes.

5:55
So if you have a length dependent neuropathy generally that will start in the toes and feet with symptoms of numbness or weakness, and then over time if it progresses and gets worse, then starts to affect nerves that are shorter and kind of moves up the legs.

6:10
If it progresses further, gets up to about the knees and at this point that the nerves that go to the knees are about as long as those that go to the hands.

6:18
And so with this sort of life dependent pattern, you can start to get symptoms in the hands as well.

6:25
So, to take a step back, what are what are these peripheral nerves? and how do we think about them?

6:30
So, basically, they're sort of like electrical wires that transmit electrical signals either sending signals from the nerve to the muscle to to contract the muscle or a signal from the skin or surface of the body to send some sensory information to the brain.

6:45
And so, in this analogy the the wire is what we call the axon of the nerve and then the insulation around the axon is the myelin sheath.

6:55
And so, peripheral neuropathy can either affect the axon or the myelin sheath or both.

7:01
And when it affects the myelin, we call it a ...

7:05
neuropathy and so, in this example here, you can see that there's sort of loss of some of these portions of myelin.

7:11
And when this happens it leads to slowing of the transmission of electrical signals that we can pick up on an EMG test.

7:19
Then, if the problem isn't the axon, we call an exon on neuropathy. And generally, with length dependent neuropathy is the problem starts at the end of the axon, and then slowly sort of works its way back towards the cell body.

7:29
And in this case, the speed of transmission is unchanged because the myelin is unaffected, but, the actual size of the electrical signal when you stimulate a nerve starts to go down.

7:42
So, um, when we think about inherited neuropathy, is I apologize, But historically, this has been kind of a mess in terms of how these are named and discussed, and so I know it can be confusing for, for patients, and it's also confusing for the clinicians.

7:58
And so sensory and motor neuropathy is an inherited neuropathy. It affects sensation and motor function is classically called ..., Marie tooth Disease. And this is named after the three positions on the right that initially described it.

8:11
And it's broken up into two main categories. Although there's types 3 and 4, but mainly, we think of type one CMT, which is ... neuropathy, so slowing of nerve impulses versus axonal neuropathy.

8:25
Just to complicate things, there's also forms of inherited rather than only affect sensation or only affect motor function.

8:31
And so if it's only sensation, we call it H S N, Hereditary sensory, autonomic neuropathy and then motor. varieties are called H and then hereditary motor.

8:41
And so there's lots of different causes of these various types, and there's often a lot of overlap. So an H and N can sometimes look like a CMT, depending on the patient or the family. So there's a lot of genetic overlap and what we call phenotypic overlap.

8:56
So again, it's kind of messy. But in general, those of us that see a lot of inherited neuropathy, kind of lump all of these different things into the larger umbrella term of CMT.

9:05
And the other feature of CMT is that it really refers to genetic forms of neuropathy that only cause problems with nerves, but don't cause problems in other organs of the body.

9:16

But there are inherited forms that are out there that do cause problems elsewhere.

9:20
And so, I listed just a couple here.

9:23
one of them that I'll be talking about later is familial MLA pie neuropathy or editor a amyloidosis, and this is it can be a sort of aggressive and severe neuropathy that can also affect the heart and can affect the eyes, as well. So that's not classified as CMT, even though it's an inherited.

9:41
So when we're thinking about whether someone might have an inherited neuropathy, there are certain sort of signs and symptoms that we look for, So well, any sort of sensory neuropathy can have numbness.

9:53
Or tingling or pain, usually inherit and drop. These tend to cause more of loss of sensation rather than these extra uncomfortable sensations.

10:00
Although certainly exceptions to that rule have been quite a bit weakness in the feet. Toes and ankles is very common.

10:09
Then one Clue can be changes in the way the feet look. So we often, as clinicians, will look for what we call high arches or hammer toes.

10:18
It's curling at the toes, and this can be suggestion of an inheritor RPO, though this on its own, does not clinch the diagnosis.

10:27
Because of the loss of muscle bulk in the legs, particularly below the knees, people can develop very thin legs, like is shown in this picture. And then the weakness, particularly below the knees and below the ankles can lead to difficulties with running, jumping, and balance.

10:46
Then later in life as the disease progresses, then you can get weakness and atrophy of the hands as well.

10:52
And so one of the clues to inherit erupting, certainly, as if other people in the family have a neuropathy as well.

11:01
So there's a lot of different ways that neuropathy can move through families and be inherited, and so you'll hear more about that in the second part of the webinar.

11:10
So when we're thinking about whether someone is likely to have an inherited neuropathy or a different cause of their symptoms, these are the sort of things that we think through.

11:19

So things in favor of inherited neuropathy, if there's other people in a family that habit, certainly parents, siblings, children, are the most suggestive.

11:28
Some neuropathy can can occur spontaneously. So a lack of family history doesn't rule it out, and there's also recessive forms that are harder to track their families.

11:39
Age of onset is another big indicator. So, generally, with CMT, and other inherited neuropathy, these.

11:46
While the symptoms might not be obvious, early in life, usually, we can find some hint that they're there, even in childhood, or the teens or twenties. So, we, we call anything that sort of happens after the age of 40 as late onset. And before age 40 is early onset and most forms of CMT, or early onset. Although, the more we learn these days with the era of genetic testing being so easy, the more we see sort of exceptions to these rules.

12:13
Another clue is that there can be often long standing foot before me.

12:17
So those curled toes, high arches can often be noted to occur really early in life.

12:24
Then we often hear the sort of subtle suggestions with difficulties with athletics as a child, So maybe someone will say that they never could really ride and keep up with their peers.

12:33
They may have at last picked for for sports activities are very clumsy are just didn't like sports in general, because they had a hard time with them, so those can be sort of subtle things that suggests that the neuropathy has been there a long time.

12:48
So, on the exam we look for the things I sort of outlined in the previous slide. So, atrophy of the muscles below the knees.

12:54
particularly the sensory loss and sometimes with CMT and farther ahead and drop these we may find more problems on the sensory exam than the person is actually aware of.

13:05
And then we look for the flip changes as well.

13:08
And then on the EMG test sometimes this can be really helpful in pointing towards an inherited neuropathy and sometimes not so much but one of the things that can be really useful particularly with ... neuropathy is what we call a uniform slowing of nerve impulses.

13:22
So what this means is that when we look at, we find slowing of the speed of conduction through these nerves. If it looks sort of the same in every nerve we test that we call that uniform.

13:32

And that usually suggests that there's kind of a problem everywhere in all of the nerves which is more consistent with an inherited process.

13:40
On the other hand, things that sort of push us away from thinking about an inherited neuropathy.

13:45
Certainly, if the symptoms are sort of rapid onset, or you know, you can kind of point to a time when they began, that suggests more something that was acquired in life, rather than inherited.

13:54
Then if there's no other reason, like a diabetic neuropathy, that can explain the ..., and that certainly pushes away from inherited diagnosis.

14:03
If there's a lot of asymmetry again, this is pretty unusual for genetic neuropathy.

14:09
And then if we're able to find some other alternative cause, like major problems with the back or the spine, that can explain the symptoms, then that, clearly, these us away from an inherited rafi diagnosis.

14:20
And then the other thing is if sort of the opposite of what I mentioned with the discussion of what we see an EMG with inherited neuropathy. If we see sort of patching it so there's some slowing of nerves on one side and not the other. Or different nerves at different speeds, that is more suggestive of something that was picked up in life rather than genetic.

14:39
As far as ... these there's not a lot of things that can be found on EMG that really push in that direction.

14:46
With the exception of maybe sometimes the the numbers from the EMG nerve conduction will look sort of more severe than what we find on exam and sometimes that can be a sign of an inherited neuropathy as well.

14:59
So to make a diagnosis of inherited neuropathy is sort of the constellation of things I mentioned, but then genetic testing is really at the core of really making a definitive diagnosis and so you'll hear more about how that works and the various kinds of results you can get with genetic testing in the next part.

15:18
So this class of diseases called CMT is really large so so far There's over 100 different genes that have been Identified to cause CMT so in this picture on the right this is only a partial list.

15:32
Within CMT, though about half of our cases are CMT one A And that's sort of what I was describing with the uniform slowing that we see and nerve conduction studies But then there's many many other forms CMT two A and seem to one X make up about five to 10% Each and then there's you know Nearly 100 that make up the rest of all CMT.

15:54
So for the most part we can't really tell the difference between different types of CMT just based on it on an exam, so they look more similar than they look different.

16:03
So CMT one a it looks a lot like CMT two A which looks a lot like CMT two D There are some exceptions to that. There are some sort of unique features of some types of inherited neuropathy, but for the most part, they they are pretty much indistinguishable when we do a clinical exam.

16:21
So if, let's say, you have a suspicion for an inherited neuropathy and you do the genetic testing, and it doesn't find a genetic diagnosis, so what does that mean?

16:30
So, it makes it less likely that there's an inherited neuropathy, but it doesn't rule it out, and the reason is because, well, we know 100 different genes now.

16:38
There's who knows how many that we haven't yet identified, and so we can't say definitively that you don't have an inherited property because we can't test every gene because we don't know them yet.

16:50
And just as a sort of points to make on this, we're still finding new neuropathy genes all the time.

16:58
And this was just last year, a paper that came out describing this new kind of neuropathy, what they call sword neuropathy.

17:06
And the reason I point this out, as it turns out, it's probably the most common form of recessive, axolotl, CMT. And so it's pretty common, But it escaped our notice for a long time, for some complicated reasons.

17:17
But, just to point out, there's still a lot of genes that we haven't discovered yet.

17:23
So, why is it useful to get a diagnosis, So what we would like would be ideal as if that led to a treatment.

17:31
So, unfortunately, with CMT, we don't have any treatments yet, and it's very active area of research, My own research and many others, but we don't have any at this point.

17:41
Um, but there are treatments for other forms of neuropathy. So I mentioned earlier this familial, amyloid polydor apathy, and so, a couple, a few years ago. Now, these two really landmark papers: describe two different sort of related treatments for this: this really aggressive form of neuropathy.

17:58

And so, this was really huge in the field, and really demonstrated for the first time that we can treat inherited neuropathy, And so, this is the kind of breakthrough that we're trying to now move towards in CMT and other forms of inherited interrupt.

18:12
Even if there is no treatment, there's, there's things that can be done following the diagnosis, so, you can participate in various research efforts to try to help all of us in the community that work on this, these diseases that help move things forward and work towards treatments.

18:26
Um, it also helps with prognosis.

18:28
So, when you get a diagnosis of CMT, or another inherited neuropathy, you kind of know what you're dealing with.

18:33
In general, that means very slow progression over years.

18:37
In general, CMTS and other headed out these for the most part, don't sort of ramp up and speed up. They sort of go at this slow steady pace throughout life.

18:47
It can also hopefully spare you from treatments that might not be needed or might actually be harmful.

18:52
So some other kinds of neuropathy is that are not inherited, can respond to things that sort of influence the immune system. And that can be great. But they also have side effects. So it's helpful to reduce your exposure to those kind of treatments, if they're not going to be helpful.

19:07
And they aren't helpful, and CMT in general.

19:12
And then, hopefully, it can give you some peace of mind just to kind of have some sense of what you have, and it can help limit further diagnostic workup.

19:21
Then as you'll hear about more, this can help us, sort of testing and other family members and family planning as well.

19:29
So, say you get a diagnosis of an inherited neuropathy. so what happens next? So, like any form of neuropathy, we sort of manage the symptoms primarily so that can be physical therapy, orthotics, ankle foot or ... is shown here, if foot drop as a problem.

19:45
And then if pain is a major component, we treat that pain with medications as we would any other neuropathy.

19:52

Then the other things you can do is connect with patient advocacy groups, There are many of them out there and you can get involved with, with those at any, any level, you would like test other family members to help them in their diagnosis.

20:09
Then there's also the participation possibilty to participate in clinical research.

20:13
And so I work with the Inherited Neuropathy Consortium, which is a worldwide effort to understand more about inherited neuropathy.

20:21
And right now, there are not a lot of clinical trials going on. But for the most part, what we're doing are what's called natural history studies.

20:28
And these don't really sound the most exciting to get involved with as a patient.

20:32
But what they really do is help to define how diseases change over time.

20:37
Because you can't really know if you have an effective treatment. You can't really know that it's working unless you know what happens if you don't do the treatment? So these are really important first steps towards moving towards clinical trials for various forms of inheritance.

20:54
So I wanted to highlight a few examples of how the research on inherited op these is moving towards clinical trials and at the end, kind of give you an example of how maybe some of the work on inherited drop, you can eventually feedback into non inherited drop the understanding.

21:11
So first, COMT one, as I mentioned earlier, this accounts for about half of all CMT.

21:17
And this form of CMT is caused actually by an extra copy, a duplication of a gene, called PNP 22.

21:23
And what research that researchers have done is basically put this genetic change into mice and then study whether they can be treated.

21:31
And what they've done is this sort of approach, similar to what was done with those earlier papers I mentioned. Unfamiliar, MLA, pie neuropathy.

21:39
So, they use what's called Antisense Oligonucleotides to try to reduce the amount, of the PNP 22 gene, and what they found, was that on the left here is sort of what normal nerves look like in a cross-section.

21:53
In the middle is what nerves look like in these mice that have been given CMT one A essentially and on the right is what they look like after they've been given this drug to reduce the genetic

dose of this gene, And so this was really effective, And this is something that we're actively trying to bring to patients as well.

22:11
CMT one X is another really common form of CMT about 10% or so, and this is actually due to a loss of a genes have called G J B one, and So in this case, what people have done in mice is use genetic.

22:26
Replacement strategies, gene therapy strategies to give back the normal genes, since it's lost in this condition.

22:32
And so what you see here on the lower right, is the sort of disease nerves in these mice, and then after treatment, the nerves look much healthier.

22:39
So again, this is something that with time, could hopefully be translated to people as well.

22:45
CMT two A is the most common form of Type two CNG.

22:50
And this has been really active research effort for many years now. And through.

22:56
Work in multiple different labs. We've come to understand a lot about this condition.

23:01
What's interesting is this is a mutation in this gene called ... or anything too.

23:06
There's actually a very similar gene called MSM one.

23:10
And what people have found now is that they've developed drugs that can sort of boost the activity of NF and one, and that can sort of compensate for the mutations in MF Into.

23:19
So this has been done in mice as well.

23:21
So in the middle panel, you see sort of the sick CMT to a mice or their nerves degenerating and on the right this is after the Mice have been given this drug to sort of boost.

23:32
The levels of the activity of an N one and the nerves look much healthier And so this again is something that we hope to bring to patients eventually.

23:40
CMT two D is uh a form of CMT is caused by mutations in this gene called ... or ..., and It's very similar to many. Other types of CMT.

23:50

So the idea is that what sort of insights we make in CMT today might really translate to other forms of CMT.

23:57
And there were a couple of papers in the journal science that just came out a few weeks ago.

24:01
So it's really really prominent journal with her with exciting findings, and what they basically found, they sort of honed in on what happens downstream of these mutations.

24:11
And they were able to use, again, sorry, gene therapy, to sort of fix this defect.

24:19
And what they found was that this is a graph of grip strength in the in the mice.

24:24
Is sort of a test of strength, the, the CMT to de Maistre and the green bar. And if they give them this gene therapy in purple, They look just like the normal mice. And so this is a really exciting findings.

24:38
In my lab, we study this gene trophy for which causes CMT to see and other forms of inherited neuropathy. And what we've found is that there's already known to be really good drugs that can block this, this gene, that codes for an ion channels.

24:52
And if we give these blockers to either flies in this case or mice, we can rescue the degeneration that happens in this.

25:01
In these animal models, suggesting that these kind of drugs might be beneficial for patients that have these mutations.

25:08
And then the last example I wanted to go through is what I mentioned before, this recent discovery of this condition called sword neuropathy.

25:15
And so, this has been a really exciting finding. It turns out that this form of neuropathy is caused by a mutation in, an enzyme that's in a sugar metabolism pathway, and what happens because of loss of this particular enzyme.

25:32
You get an accumulation of this sugar, called Sorbitol, within nerves, and this orbital is toxic to the nerves.

25:41
What's interesting is that it was already known that Sorbitol is toxic to nurse because this is something that accumulates in diabetic neuropathy.

25:48
And so people have already been focused on developing drugs, two blocks or baton production for diabetic neuropathy.

25:55
And now we have another situation where sort of it all seems to be causing nerve dysfunction.

26:00
So this is exciting on multiple levels.

26:03
There's, we think a large number of people that have inherited neuropathy, that hopefully can be treated with this kind of approach, but it also shows us that there's sort of overlaps between inherited neuropathy and other neuropathy like diabetic neuropathy.

26:17
And it gives us hope that as we study these sort of inherited conditions, the ultimate goal really, you know, it's not just to treat the patients that have these genetic changes, but also learn enough about peripheral nerves and peripheral neuropathy that we can come up with, treatments that other people can, can benefit from.

26:34
So, that's all I have for now, and so now, I will turn things over to, to Christie to take you through some more about the genetics.

26:46
Oh, thank you.

26:49
This is the picture of the, the fly model, they generated that, that, showing that these drugs work within the, within an animal model, I'm sorry, Now I'm done.

27:00
Perfect, thank you.

27:01
That was, that was fascinating, and, again, great introduction. Now, we'll turn it over to Cristi Smith, who will give her perspective as genetic counseling and testing.

27:16
Thank you.

27:18
Thank you for having me here today. I'll go ahead and just jump right in.

27:30
It's not progressing my slides.

27:35
Up, there we go, OK. That's a delay. Alright.

27:38
So, as Doctor McCray had mentioned, there's many different types of hereditary neuropathy these which I won't spend a lot of time going over today, but just to kind of re-iterate, most Common Cause Is sarcoma a tooth disease, which is also called hereditary motor and sensory neuropathy.

27:55

We also know that there's other forms of neuropathy's as well that fall into either just motor neuropathy versus sensory.

28:02
There can also be episodic forms such as H N Cube D, which is the hereditary neuropathy neuropathy with liability to pressure policies where there's episodic attacks of the neuropathy is that are seen.

28:16
Then, as doctor McCray I'd mentioned, there's also these complex forms as well, where you can see neuropathy plus other symptoms that can can affect other organ systems, and these are more commonly disorders that you might see, say, in our General Genetics clinic.

28:34
And also as Doctor McCray had mentioned, there are certainly many challenges to diagnosing Hereditary neuropathy is first we know that there's many genes that cause these conditions. There's hundreds of genes associated with these hereditary neuropathy is sometimes we can the diagnosis is fairly straightforward, but oftentimes we're doing larger gene panels or much larger genetic testing to identify an underlying genetic cause.

29:01
And we also know that many of the symptoms are non-specific and can overlap with each other. We know that even within the same family with it, with the same genetic condition even with Charcot Marie Tooth Disease that there can be a range of symptoms where some people are are affected pretty mildly versus others are affected more severely. And we don't totally understand that but we know that there's many genetic and non genetic factors that can influence that.

29:28
And again, as doctor McCray had mentioned, there's often no family history that indicates the inheritance pattern, with Ashoka Marie tooth disease types 1 and 2, And I'll talk about inheritance in a minute. Typically, those are autosomal dominant disorders where we might expect to see a family history. But not always if the condition occurred for the first time in that an individual, and was not necessarily inherited, but there'll be passed on.

29:52
But, with other forms, with recessive disorders, parents may be carriers, and there's no no family history. And we may see a person who's the first one in the family to have the symptoms of the disease.

30:05
And also as doctor McCray and mentioned as well. We know that there's limitations to non genetic tests as well that the nerve conduction studies, the EMG and the nerve biopsies aren't perfect. They're just one piece of the puzzle to try to come up with a diagnosis.

30:21
So in terms of the importance of a genetic diagnosis, certainly the main main reason is to identify a cause to help identify prognosis moving forward, Many patients have gone through a diagnostic odyssey to try to figure out what's going on.

30:36

Medical management can certainly be modified as well as Doctor McCray had mentioned. You know, that once a diagnosis is made for many of these disorders, they're supportive therapies, but newer, gene specific gene therapies that are going on.

30:51
And also helping to rule out non genetic causes because we know that there's other conditions as well that can mimic hereditary neuropathy such as having Lyme disease, diabetes, vitamin B, 12 Deficiency.

31:04
And ..., which is more of an autoimmune disorder that's treated very differently.

31:12
And we also know, that I had mentioned as well, and doctor McCray had mentioned, there's gene specific therapeutics that have been on the horizon.

31:21
So with these RNA interference studies specifically for the TTR associated amyloidosis, TTR is the gene, that's the cause of this condition.

31:31
We know that there's enzyme enzyme replacement therapies and oral chaperone therapies for conditions such as Fabry Disease, which is more of a multi systemic disorder. But can also cause neuropathy.

31:44
And, also, as Doctor McCray had mentioned, some of the clinical trials that are ongoing for a PMP 22, which is associated with sarcoma, A tooth disease, type, one, A.

31:55
And sort of where I kinda come in, it's maybe the first point, but certainly the last three points here as a genetic counselor. So, helping to identify, you know, once we do make a diagnosis, identifying at risk relatives to other people in the family that are at risk to have the same condition with the recurrence risk is. So, especially for younger people that are part of reproductive age, what's the risk of having another child with this condition?

32:20
And then, also, what?

32:21
What are the reproductive options, which I'll talk about a little bit more detail later, but this can include prenatal screening and also therapies such as: pre-implantation genetic testing that's used in conjunction with in vitro fertilization, which is essentially screening embryos, then also psychosocial benefits as well. Again, many of these families may have gone through a direct diagnostic odyssey of many years of not having a diagnosis, and finally, having an answer can really be. You know, a really important thing for families oftentimes, are finding that they're wanting to have a positive result versus a negative result, to have more clarity.

33:03
So what I do is a genetic counselors are working in conjunction with the doctors. So I'm not performing physical exams or EMG or anything like that but reviewing their medical history, how that patient was thought to have that diagnosis of a hereditary neuropathy.

33:20
And then also collecting family history information.

33:23
So not many doctors take a full family history. I think doctor McCray and others are pretty good at doing that. But most people, most times when you go to your physician, they're not asking more detailed questions about extended family members.

33:36
So what I'm creating a similar here to a pedigree down at the bottom, so circles are females and squares or nails.

33:43
So drawing out a patient, siblings, parents, grandparents, aunts, uncles, cousins, at least going out at least three generations.

33:52
And by drawing a pedigree, even if there's no one else that's affected in the family. It does help to identify the possible inheritance pattern, and then identifying who else in the family can be at risk.

34:04
Um, and this also helps to figure out what's the most appropriate tests to order, which I'll talk a little bit more later. But whether we're thinking of doing targeted testing for specific gene variant that we know this in the family is the genetic cause whether we're considering a gene panel where we're looking at multiple genes associated with hereditary neuropathy.

34:25
Brave and whole exome sequencing where we're looking at all 20,000 of our genes. And it's also important to that if any genetic testing has been done in the family, to try to obtain a copy of those genetic test results. Because those are important that instead of doing this much this much larger testing, we would only test for that specific variant and the family, assuming that that's the cause for the neuropathy.

34:49
And then, again, as I had mentioned, going, thinking about the reproductive risks and options in most other family members.

34:58
So, to take a step back, some of these terms are, I'm sure, a little bit foreign and jargon, E so, when we think about genes, genes are the instructions that tell her body what to do. We all have the same genes that just the selling of the genes are different, and we all have about 20,000 genes in our body.

35:15
And, for most of our genes, we have two copies. So, we inherit one copy from our mother and the other copy from our father.

35:22
And so, genes are located on chromosomes, and chromosomes are packaged within cells of our body that have a nucleus set far red blood cells that don't have a nucleus.

35:32

And we all have 46 chromosomes or 23 pairs. So our genes are scattered along our chromosomes.

35:39
And again, genes are the instructions that tell her body what to do. So they're made up of a series of letters, A's, C's, G's and T's, that code for proteins.

35:48
So kinda the way that I always say to patients to kind of think about this is, when we're doing genetic testing, If we're looking at day, 30, 100 genes were reading through 30 or 100 books. To try to find a misspelling. A misspelling, a missing or extra page within that book, and Missing paragraph, and missing chapter, on something that makes that book unreadable or makes that G not work properly.

36:10
So really, it's almost like trying to find a needle in a haystack and then once we can find that needle in a haystack, then the testing is much more targeted and directed for other family members.

36:22
So when we refer to a mutation, or a variant, or a pathogenic variant, or a disease causing variant, it's essentially a change in the coding of the DNA within that gene.

36:37
So in terms of inheritance patterns, these are the different inherited inheritance patterns that we think about for family. So, with autism, will dominant disorder is kind of going back to, we all have two copies of most of our genes within our body. We inherit one from our mother, the other, from our father.

36:52
So having a dominant disorder is where having one non working copy of the gene is sufficient to cause the disease.

36:59
And that really describes most forms of hereditary neuropathy that we think about.

37:04
So whoever has a dominant disorder, there's a 50% chance to pass it on to the next generation. So you either pass it on or you don't. If you pass it on, the next generation is at risk, and could also pass it on.

37:16
If you don't pass it on, it stops there.

37:18
Certainly, one missed misconception is that these disorders, genetic conditions can skip generations, and they don't skip generations with dominant disorders. It can just be more confusing that there's certainly a lot of variability in the symptoms that can develop in the age at which someone develop symptoms. So it may seem like it's skipping a generation, but it is being passed on.

37:41

Um, then, with autism or recessive disorders, that refers to, again, going back to we have two copies of each gene. So both copies of the gene are not working. So you inherit one non working copy copy from your mother and the other from your father. And each parent is usually a carrier for working and a non working copy. So then they don't have symptoms of the disease.

38:03
But when each parent passes that on, and a child inherits tune on working copies, then they have that condition.

38:10
So, typically, with autism or recessive disorders, we don't see a family history of that condition.

38:16
And we, if we do see a family history, it would likely be in siblings of the same generation.

38:22
And so, typically, there would be a 25% risk of having another child with that same recessive disorder.

38:29
And you can kind of see down here that I have shown a pedigree, and you can see very subtly that there's two lines drawn in between these two individuals.

38:39
And this denotes Consanguinity, which is also referred to as just shared relatedness.

38:44
So we know that if two people have a distant cousin or related to one another, they're more likely to share more genetic traits in common, and so, therefore, more likely to have a child with a recessive disorder, Abuse.

38:59
Dots in the middle here signify that both parents are carriers. And then, these people colored in would be affected and that people not colored and would be unaffected.

39:09
And if they had another child, there would be a 25% risk to have another affected child.

39:16
With excellent disorders that has to do with the X chromosome. So, as I mentioned, we all have 46 chromosomes, 23 pairs. They're numbered 1 through 22, the last set of chromosomes as our *** chromosomes.

39:28
So women have two X chromosomes men, have an X and a Y, and we know that there's genes on the X chromosome that can cause hereditary neuropathy.

39:38
Less common, but in people that have those, typically males are more likely to be affected, and females, either could not be affected at all, or maybe more mildly affected.

39:50
And it may look autosomal dominant and families, because you can see it being passed on from one generation to the next.

39:56
But one feature of X linked inheritance is that there's no male to male transmission, because all men pass on the Y chromosome to their sons, and their X chromosome to their daughters.

40:08
Um, and so as I had mentioned, males and females can be affected differently with excellent disorders.

40:15
And then there's also mitochondrial inheritance which is also a less likely.

40:19
Less common cause of hereditary neuropathy is but the mitochondria are a separate portion of the cell. And so you have within the nucleus of the cell, the chromosomes with your genes and your DNA, outside of the nucleus of the cell. you have what's called the mitochondria. And the mitochondria are responsible for energy production. And not just, I feel weak or tired. But feeling the energy for all of the major organ systems, including your eyes, your ability to hear, your brain, your heart, your liver, your kidneys.

40:50
And so often with mitochondrial disorders, we would expect to see multiple organ systems and update, including the central nervous system.

40:56
We've been seeing around 50, sometimes the property is the only source system organ system that we see affected, sometimes there's others as well.

41:06
But essentially with mitochondrial disorders, they can either be caused by genes within the nucleus or the mitochondria have their own set of instructions, 37 genes.

41:17
So there's a separate test that we can look at the mitochondrial genome, and the mitochondria are only inherited from your mother.

41:25
So typically in families where we suspect a mitochondrial disorder, we'd look for the mother side of the family.

41:33
There can also be variability throughout the generations, if and when people are affected for more complicated reasons that I won't go into today.

41:41
And then of course there's multi-factorial inheritance where there's multiple genetic and environmental factors that we're still kind of learning about at this point.

41:52
So there's many different types of genetic tests. They're not all created equal. Certainly we can do genetic testing through a blood sample or a saliva sample. But again, there's different ways that we actually perform the test.

42:03

But as I had mentioned earlier, there's targeted testing, but there's a known variant within the family cell.

42:09
We find in a spelling within that book, or that Gene, that makes that book unreadable or that Gene that work.

42:15
And so with that specific misspelling, we would target that and other family members.

42:19
So we might say, in book a page, 50, 576, paragraph three, Word five, there's a letter A that got changed to a G So let's look for that specific misspelling and other family members.

42:31
And again, it's helpful to have a genetic test report for someone that's tested positive.

42:38
Then, there's larger gene panels that cover many hereditary neuropathy genes.

42:44
And so, oftentimes this is what we're doing. when someone has a diagnosis or they are effective. They have symptoms and we're trying to figure out a molecular diagnosis by doing genetic testing, where sometimes it can be straightforward where we might suspect CMT, one A, but oftentimes we're doing these much larger panels, just because of that overlap of symptoms.

43:06
Um, as Doctor McCray had mentioned earlier, so negative genetic test results do not entirely rollout for editorial neuropathy. It makes it less likely, but we don't know everything in genetics.

43:17
So of the 20,000 genes that we all have, we understand the function of about 5000 of our genes in relation to human disease.

43:24
So that means that the other 15,000 of our genes, they're there, they exist, but we don't know what they do and we haven't connected the dots between those genes and humidity.

43:33
So, we're constantly learning about these new disease genes that a genetic test today could be completely different in the future as we learn more genes that are being added to these panels as Doctor McCray had talked about and some of these newer genes that are being discovered.

43:49
Um, and so, and then we also know that there can sometimes be an overlap between hereditary neuropathy and other musculoskeletal disorders.

44:00
So certainly, this is, you know, I leave up to the neurologist, but just kind of keeping in mind that, you know, if we get a negative genetic test results, are, we ordering right test, so that's something else to think about.

44:14
And as I mentioned with mitochondrial disorder.

44:17
So we can do a blood test or buckle test, which is basically just a cheek swab or saliva versus a muscle biopsy.

44:26
and this is essentially because when we're truly looking at the mitochondrial genome, these 37 genes, we can certainly look at a blood or saliva sample to identify a genetic cause, but sometimes it's not there.

44:38
And the reason for that is because all of the genes that we have in our body, if we identify an inherited mutation, it exists in all of the cells of our body. It's something that we're born with. It doesn't change over time. With the mitochondria.

44:51
It's a little bit differently that different cells within our body can have more or less mitochondria that are affected.

44:59
And oftentimes we see more mitochondria effected in Oregon systems that are, that we see symptoms. So, for example, if someone has a muscle disease or a nerve disease, they might have more of their mitochondria that are affected there, versus, if you look at their blood, that's not affected. We may not see the, the gene alteration there. So certainly thinking about a sample that we're using also matters.

45:23
So we need a biopsy sample from that specific tissue if we don't make a diagnosis through blood or saliva.

45:33
And then with whole exome sequencing, which I'll talk a little bit more, so, again, as I had mentioned, we all have about 20,000 genes.

45:41
And genes only make up about one to 2% of all of our DNA.

45:45
So, the rest of our DNA, the 98, 99% of our DNA, we know that it's there, and it exists. But we're still trying to understand what the rest of our DNA does.

45:54
There's another test called Whole Genome Sequencing, that is used to look for, look at all of our genetic information.

46:02
But, again, even though we have the technology, we're still learning and genetics. So, we still don't know everything. The testing is is definitely getting better, but our knowledge we're still trying to catch up.

46:13
Um, so, again, as I mentioned, when we're doing whole exome sequencing, a negative result is negative today. It's not negative forever because we only understand what about 5000 of our genes do.

46:25
Oftentimes, when we're doing collection sequencing, we have the option, in the Future, to do what's called a re-analysis.

46:32
So, a year or two years from now, we can ask the laboratory to look at the data again, to see if there's a new gene that we learned about, that the lab didn't know to look for before.

46:42
Um, so, we're never really closing the book whenever we get a negative genetic test result, unless a non genetic diagnosis is made.

46:52
Then, in terms of the importance of trio's, what this means is that when we're doing whole exome sequencing, it really is like trying to find a needle in a haystack.

47:01
So, it's most helpful to interpret the test result if we can include samples from both parents.

47:05
So, mother and father, Certainly, that's not always possible for various reasons. Sometimes we may choose to include other family members in the testing, but standard Lee, including both parents it's helpful because no inheritance pattern helps the laboratory to better further funnel down the testing.

47:22
And with whole exome sequencing, I should've mentioned that, even though we're looking at all 20,000 genes, we're only looking at those genes that matter in terms of the diagnosis.

47:32
So, whole exome is not looking for all health problems.

47:36
It's it's looking at someone's medical history so neuropathy and then funneling the testing down to look at only neuropathy genes to make that diagnosis.

47:47
Then, secondary findings refers to information that is sort of secondary information that we can find on exome and it's usually optional.

47:55
So, you can either choose to know this information or not, and this is a list of over 70 genes the American College of Medical Genetics has put together that are medically actionable, so whenever you're undergoing exome, you have the option of knowing if you have, say, an alteration, in a gene that predisposes you to breast cancer or colon cancer.

48:16
And the thought behind this list of secondary findings of these, these are all tradeable disorders, so there's something that we can do different about the outcome. So usually conditions that are not tradable like Parkinson's disease, or Alzheimer's dementia, Huntington's disease would not be included on this list.

48:34
And again, you have the option of knowing or not knowing this information.

48:40
And whole exome is not perfect, so it can't detect all genetic disorders. So there's certain repeat expansion disorders and your doctor McCray had mentioned, that's Canvas disorder.

48:51
So repeat expansion just means that there's a series of letters, A's C's, G's and T's, that are repeated over and over within the gene.

48:58
So if there is a repeat of certain letters, this test is not able to find that.

49:03
A good analogy is that, you know, for reading through a book and the word da is copied over and over again on one page of the book. The whole exome sequencing is not going to catch that, because it's doing a spell check or Lyft are looking for missing or extra material. It's not looking to see if there are certain letters that are re or words that are repeated over and over.

49:26
Exome can't look for non coding variants. So.

49:29
but this means a good analogy is that, if you're reading through a book to try to find a misspelling, if there's a misspelling in a word in the margins of the book, exome cannot detect it.

49:40
So that's something that's typically identified on a genome and there are certain deletions or duplications within genes that exon can't capture. So again, genetic tests, it goes, isn't perfect.

49:53
And just to kinda touch briefly on the reproductive risks that we could identify.

49:56
So essentially, if we make a genetic diagnosis, we know that this for people that are of reproductive age, that they can use this information to make different decisions either prior to or during a pregnancy.

50:09
So during a pregnancy, prenatal diagnosis is done by either a CVS or an amniocentesis that can be done at different gestational ages.

50:17
These are diagnostic procedures.

50:20
And then we also know that prior to a pregnancy, that couples of reproductive age can go through fertility centers and go through the process of in vitro fertilization.

50:31
And then take the extra step of testing embryos for that specific gene that's causing that disorder. So if that CMT Type one A, we could look for the PMT 22 duplication within the embryos and then put back the embryos that don't have that duplication to then you're guaranteeing that you're not passing on this condition to the next generation.

50:53

Of course, there's options for adoption, embryo adoption, egg or sperm donor donation, and typically this is discussed via prenatal genetic counselor. I'm not a prenatal counselor, so I would probably refer these patients to one of my colleagues at Hopkins.

51:14
And then just a couple of points about, you know, what I do as a genetic counselor.

51:18
So, yes, certainly, I think, it's easy to order a genetic test, but interpreting it can be difficult, certainly with a positive result, it may be straight forward in terms of explaining that diagnosis or negative.

51:31
We don't have an answer, but, again, genetic testing isn't perfect, and we don't know all of the genes that cause genetic disorders, but we can also find uncertain test results. So that means we find in the spelling within a gene but we're just not sure if that misspelling just disrupts the function of that gene and causes that genetic disorder.

51:49
So, it's not always black and white, positive, or negative. Sometimes we're getting these uncertain test results that we just don't know.

51:56
And it can be helpful in those scenarios to test other family members to see how it's being inherited in the family, especially if there's other affected individuals seeing that variant segregates with the disease.

52:09
And it's also really important to that for the condition that we're thinking about, that anyone that we're testing in the family has a neurological exam.

52:18
They are trained neuromuscular specialist such as doctor McCray to help identify, did. They have the condition that's associated with the gene variant that we're testing them for.

52:31
And then, of course, their psychosocial effects. So I'm, I'm a trained counselor, and so talking to these families, not only about their test results, or how it has implications of family members and genetics and for genetics education, but thinking, just talking through, how are they hoping with this, you know, diagnosed or even an undiagnosed disease. Which can be very challenging. Or once you receive a diagnosis, how are you making sense of that within the context of your own life?

52:57
Talking to other family members.

52:59
Thinking about these reproductive options, treatment's, finding support groups.

53:05
And I think there can be other issues as well, Such as, you know, guilt as to thinking about that. People pass it on to the next generations, are talking about. You know what that means. We all pass on. Lots of things to our kids are good things, too, so, kind of putting it in context.

53:21
And also just thinking about what are the relationships with other family members? Everybody has different relationships within their family, people that they talk to, don't talk to. Some people are adopted. Some people just don't know certain sides of their families to that can certainly be challenging as well, especially if they receive an uncertain test result, and there's just information about the family history that we just can't uncover.

53:47
And just some basic information, as I mentioned. So genetic testing can be done on blood saliva buckle, which is a cheek swab or biopsy tissue.

53:57
Now, in times of ..., certainly doing a lot of telemedicine to sending kids to people's homes where they can just fit into a tube, send it back to live, the EDX, that's usually pretty quick.

54:07
Um, genetic test results, it really depends. Sometimes they can take anywhere from a few weeks to a few months. Usually, whole exome sequencing takes longer versus, you know, targeted testing, looking at a specific variant we can often find on can get that information back pretty quickly.

54:24
And all of the genetic testing that I'm doing is clinical testing that's done in the laboratory that has CLIA certification.

54:32
It also is subject to the HIPAA rules and regulations.

54:36
So, protecting your information, that it's not being sold to outside companies, or things like that, 23 and me, is very different from the clinical genetic testing that I do. So 23 and me, as direct to consumer.

54:51
So there's typically not a physician in ordering it. Typically, this is more for fun information, although there is more medical information that's being put it on 23 and me.

55:00
I'll just say that I'm a little bit hesitant to use those companies because they are selling data, and it's not always, you're not always getting the whole picture. So I think it can be fun to do 23 and me or ancestry dot com, but it certainly doesn't substitute for good medical care.

55:19
And just wanted to mention very briefly about gina. This is the Genetic Information non discrimination Act. which typically applies to unaffected individuals. So this would be for family members of someone that has an hereditary neuropathy with a genetic cause.

55:34
So anyone else in the family that could be at risk?

55:37

What this law says is that it protects against discrimination from your health insurance and your employer based on a genetic test result, but doesn't protect against the potential discrimination with life insurance, disability insurance, and long term care insurance.

55:51
So, oftentimes I tell patients that if you're unaffected and you're doing testing, that is more pre-symptomatic testing to see.

55:59
Could you develop symptoms in the future to go ahead and take out some of these other policies. Because it's not like these plans can drop you. It's more just if you're taking out a new policy or additional coverage, that these insurance plans could ask you if you have genetic test results, and can underwrite based on information.

56:20
And I don't want to get too much more time. I only have two slides here. I want to save some time for questions. But just a plug really quickly that genetic counseling can certainly be helpful.

56:29
Regardless of whether or not you've had a positive negative or an inconclusive genetic test, just kind of thinking about new testing options if you've had negative testing the past kind of understanding the implications of a result, positive or inconclusive, variant interpretation for Missive test results.

56:47
This is certainly very complicated and I think about this all the time, updates to genetic test results because we know that that can change all the time.

56:56
Um, then just thinking about who's ideal in the family to have genetic testing. So, typically, when we're doing genetic testing the needle in a haystack testing on someone who's affected.

57:07
And then testing, unaffected relatives, once we identified that gene alteration.

57:12
And also having a neurological exam is, it's very important to just to assist with the genetic test results.

57:19
Typically, you can find a genetic counselor through, like your primary care doctor. You can ask for a referral, but you can also go to ... dot org, which is our professional organization. And you can find a genetic counselor there in your area by entering your zip code.

57:35
I will stop there. Thank you.

57:46
Can't hear you, Nancy?

57:54
Yeah, yeah, I think you're muted.

57:58

Alright, doesn't the organizer always forget how to work the platform? Sorry, everybody. Thank you, Kristi. Thank you for all the information. You all have given us such great information with some great questions. So, we're going to impose a little bit longer on your time, if you don't mind. Anyone in the audience, we'd love to have you stick around for some. A couple of questions. This will also be recorded and you'll be able to hear it later if you can't stay around. But I want to jump into some really good questions that come have come out.

58:30
I guess I will ask Kristi first, but please, doctor McCray, step in if you have a viewpoint on it, we had a couple of people who have some of the symptoms that you've described.

58:47
They've had tests years ago about, uh, with hereditary or inherited neuropathy is and they were negative, has the testing gotten better, should they go be tested now and what would be their first step?

59:04
Maybe start with Christy and then, doctor McCray, you can get from the doctor's perspective?

59:10
Yeah, definitely. I mean, we're discovering new genes all the time. Even within the last couple of years, I've had people that have had testing, just, you know, a few years ago and the labs have updated their panelists and there's more genes that have been discovered. So, yeah, I think that there's definitely value and inquiring about additional genetic testing options that are available and certainly having a copy of your test report to view to see what testing you've had done to make that comparison. And, again, you can either go through your doctors, you know, for a referral, or talk to your neurologist who is, you know, kind of aware of a lot of this genetic testing to, I know, doctor McCray, does this testing, a lot on patients.

59:47
OK, so that is going to be my next question, doctor McCray, do they go to you, is the neurologist, or how does the patient start?

59:55
Yeah, I think, I think you can probably go either direction.

59:57
I think it's helpful, as Christy mentioned, for the neurologists to kind of settle on a sort of category of genetic diseases that we're thinking of, and that helps us guide. Most of the testing we do is based on panels of related conditions.

1:00:12
Whether it's inherited neuropathy or myopathy, things like that, have separate panels, and so the neurologist can really help to, two, move things in the right direction.

1:00:22
Having a genetic counselor involved is also very helpful.

1:00:26
But you don't, people that see a lot of inherited not being like me would, would often order the genetic testing directly.

1:00:33

Um, and I totally agree that If you've had had genetic testing in several years, it's worth sort of updating it, just since I've been doing this.

1:00:43
I've seen the panels, even in the last few years, go from 70 genes to 100 plus genes, and not just super rare.

1:00:50
No forms of neuropathy, but some that are relatively common.

1:00:56
I think it's worth an update if it hasn't been done in awhile.

1:00:59
And is it something doctor McCray, that stuns standard if somebody has been diagnosed with small fiber neuropathy or another form of neuropathy, is there any likelihood that it could be hereditary? And surely, they discuss that, they're worth their neurologist as standard practice.

1:01:18
I wouldn't quite say it's standard practice, but there's not a lot of downside to doing it in the right clinical situation.

1:01:24
So I personally have a pretty low threshold. So I sort of outline those things that I think about that make inherited neuropathy more or less likely.

1:01:33
If I, you know, I don't have to have all of those to send genetic testing if I have a few.

1:01:37
And it's often worth doing, partly because the cost, the difficulty of doing it is has come down so much now that No. And I've been surprised by situations where I had a low suspicion and I found a genetic cause.

1:01:55
I wouldn't call it standard of care, but, but I don't think everyone should have genetic testing.

1:01:59
But but a lot, you know, I have a very low threshold to two to send these panels, OK.

1:02:07
And if somebody has, if a patient has peripheral neuropathy and I guess all separated, you went through it very clearly, Christie with people who have hereditary neuropathy.

1:02:22
But maybe you can sum it up again, and maybe doctor McCray, for general patients, how likely are they to pass it to their children if you know what someone wants to know, as they have three sons? Or they get peripheral neuropathy?

1:02:36
What is, what's the likelihood?

1:02:40
And maybe you can start on one, either on hereditary neuropathy and the like or the likelihood of those conditions?

1:02:49
The cause peripheral neuropathy and then maybe doctor McCray, you can follow up again on, you know, does a peripheral neuropathy patient have to worry about their kids?

1:03:00
Yeah, I mean, I think the first step is seeing an ...

1:03:02
and having, you know, all of the appropriate exams and, you know, imaging to make sure that we're sort of in the right place. And then we need to do the genetic testing, make sure that we're ordering the right test and identify that underlying genetic cause.

1:03:17
And really we don't know the inheritance until we have a diagnosis once we have a diagnosis. Based on what we know about that gene we can say that this gene has an autosomal dominant inheritance, recessive inheritance, excellent, et cetera. And then we can give more specific information about the rest of passing and on, So whether it's a 50% risk of 25% risk, that matters what their partner has, X, linked, mitochondrial, etcetera. So it's kind of hard to answer the inheritance question without having a known genetic cause.

1:03:46
OK, and then on the flip side for that, it's in general peripheral neuropathy.

1:03:52
Doctor McCray, should a parent worry about their kids, adult, kids, or otherwise?

1:03:59
I think if, if the neuropathy is sort of late onset late in life and doesn't have many of the features that suggest that it's inherited neuropathy, then you know that the likelihood of it be.

1:04:14
I wouldn't say it would be passed on directly but there may be some sort of risk factors that run in the family that put it.

1:04:21
But other family members had a little higher risk than the average person.

1:04:26
But the absence of a strong suggestion of inherited Roxie, then you know.

1:04:35
I wouldn't worry too much about passing that on OK. That's good answer. That's I'm sure a relief for many people.

1:04:43
Christy, this is a very interesting question and very general do you see more men or women with hereditary neuropathy is a view through through your practice do you notice that that kind of a gender difference or anything, a related that comes that strikes you, or has struck you?

1:05:06
Not that I've seen. I'm sure doctor McCray can probably answer from his experiencing all of these patients, but I'd say the LA Gender differences as if you're thinking about like an X linked disorder that affects men and women differently. But, the majority of these hereditary neuropathy or dominant and that affects men and women equally, as does recessive inheritance.

1:05:25
OK, have you seen a difference?

1:05:28
Doctor McCray, I don't think so.

1:05:31
Now, um, see. even mix of both. Both inherited neuropathy is and not inherited Rocky's men, and women are equally mixed.

1:05:40
OK, well, so, so, it really it can it really is dependent upon this about having it identified in the test results itself?

1:05:51
Yeah, I'd say 1 1 really active area of research is trying to understand some people may have a diagnosis of idiopathic neuropathy, meaning that they've gone through testing for things. either genetic or non genetic that typically costs dropped and came up empty.

1:06:07
And so they don't have a clear reason for having neuropathy.

1:06:10
Sometimes, that's a constellation of lots of things.

1:06:13
But we also believe there may be at least not a it may not be genetic.

1:06:17
In a pure sense, whereas 1 1 gene causes the problem, but it may be a mix of sort of genetic risk factors, And so there's a lot of research to try to identify those genetic risk factors.

1:06:27
And what I was sort of hinting at with that soy drop the example, is we think, you know, maybe there's some overlap between genetic risk factors for idiopathic neuropathy and inherited neuropathy, like CMT. And as we sort of study those together, they sometimes the lines blur a bit.

1:06:44
Now, that was one of the questions we have a lot of patients with idiopathic neuropathy and they are curious should they be tested? Should they not be tested?

1:06:54
And I guess, maybe to address that issue is it's a conversation with their neurologist's first. Is that correct?

1:07:03
Yeah, I get a lot of referrals that ask that question, that type of question, where, no, there's, there's some features that suggest that that could be dealing with an inheritor off the versus others that suggest maybe it's not.

1:07:18
And so each case is different.

1:07:20

and it's kind of, it comes down to taking the whole, the whole picture and deciding on how likely or unlikely it is, that there could be an inherited process.

1:07:30
Then, again, you know, if I have a low threshold for, for doing the genetic testing, because I don't see a huge downside to it these days, At least, used to be that a lot of these, even the limited genetic testing panels that were available were very expensive. That's not the case anymore.

1:07:46
All right.

1:07:48
Going on, these disorders are common. They're sort of like, pan ethnic. So, they're not seen and typically, you know, certain ancestries and, you know, as a genetic counselor, I asked about, Ancestry. What countries are your family from? And we know that there are some places in the world that have a preponderance of certain genetic disorders just, you know, for different reasons of, you know, populations or having children with people that you're, you know, related to.

1:08:13
But there's not specific.

1:08:15
I mean there can be but it's it's not common that we see selfishly.

1:08:21
That's helpful.

1:08:23
Can a patient have small fiber?

1:08:26
Neuropathy cannot ever be a An inherited neuropathy and do you see people with more than one type of hereditary hereditary neuropathy?

1:08:38
So there are credit doctor McCray first tariffs or as I was gonna just that one myself. That's OK.

1:08:44
There are there are some genes that are known to cause pure small fiber neuropathy so there there tend to be ion channel genes that control the sort of electrical transmission through particularly the pain sensitive nerves and so that is definitely a situation that can be inherited.

1:09:02
Um, A lot of times small fiber drop is not, but that is that type of neuropathy does not exclude it being genetic and then I guess to Christie, do you see, is it common or can you patient have more than one kind of inherited neuropathy?

1:09:23
Do you see across across some sort of cross sector of types of neuropathy?

1:09:31
Yeah, I mean it's not super common. Typically, you know, we see one type of hereditary neuropathy in the family, but in genetics, we see it all the time that you can have 1, 2, 3, 4 different genetic disorders.

1:09:42
I think I've seen a patient with five months. So, I mean, we used to think in genetics, there's one genetic disorder that you have, but we know that that's certainly not the case. And certainly, in situations where parents are related to each, others, share more genetic traits in common, there's definitely a higher chance of having children with more than one genetic disorder.

1:10:02
So, to answer your question, I'd say it's not common, but maybe more common than what we think, OK, and then to close us out, because everyone's been very generous with the time, I'd love each of you to perhaps give us a glimpse into the future where you see genetic testing and and gene treatments as being beneficial for all patients with peripheral neuropathy. From your different perspectives and your, your areas of expertise.

1:10:35
I don't know if you want to start, Christy, or doctor McCray, you we want to start this time. Either one.

1:10:42
You can start OK.

1:10:45
I guess I would in the you know 5 to 10 years. I would.

1:10:48
I would picture a couple of things so 1 4 People that have genetic neuropathy I think will have a larger set of genes to look for, but I hope we'll be enrolling some fraction some some specific types of Neuropathy is into clinical trials, whether they're gene therapy trials or other trials that get at specific mechanisms of the disease of certain kinds of neuropathy.

1:11:13
I would love to say that I expect to see a general treatment for all kinds of neuropathy, but I don't think we're, I don't know if that's right on the horizon, But I think there's going to be sort of what we call precision medicine for CMT, where certain types, where we have a good understanding, can be treatable.

1:11:29
And then, I think four for non genetic neuropathy, I think what will will, I hope, in the next 5 to 10 years is we'll get more of a sense of results from things that we sort of these large scale tests of genomes.

1:11:46
And kind of we call lipid, omics, metallic, minimal metabolomics And all these omics kinds of tests.

1:11:55
To really start to understand what are the complex factors that lead to idiopathic neuropathy so that we can better diagnose it and better understand sort of each person's neuropathy. And then, hopefully also that will lead to some ideas of how to treat those.

1:12:11

Different forms of neuropathy, I think Idiopathic neuropathy is probably lots of different kinds of neuropathy that we don't understand, and I think we're going to make progress in understanding those.

1:12:21
Terrific.

1:12:22
That's terrific. And, and, Kristi, from your perspective, where do you see all of this testing and knowledge going?

1:12:31
Yeah, and I think I echo a lot of what doctor McCray said. I think definitely, you know, our knowledge of genes, and the genetic technologies is changing all the time.

1:12:40
And so, like I said, we only understand 5000 of our 20,000 genes, There is going to be more gene discoveries that genetic testing is going to get faster, cheaper, better, that, you know, we can do a whole Ex-Im's now. But I think, you know, we're starting to do whole genome insurance is not always covering it, but I think that it's definitely something of the future. I don't know that we'll do it for everybody, but I think we'll have better diagnostic tools in the future.

1:13:04
And definitely, in terms of clinical trials, I think, you know, doctor afraid of the cutting edge of that. But I think what many other genetic disorders was doing gene therapies and these ASL therapies, have kind of set the age that, I think, we're definitely moving in that direction of more of the precision personalized medicine that there's not really a one size fits all, and doing more targeted treatments based on the underlying genetic cause.

1:13:26
I'll just add one more thing, if I can.

1:13:29
I think in the past several years, there's been a bit of a shift in the way that pharmaceutical companies think about diseases, And so they've shifted somewhat away from common acquired diseases, and moved towards genetic diseases with a hope, I think that, you know, when you have a genetic disease, you have a really good foothold on what's going on and how you can treat it.

1:13:51
And then once you start to establish those, those strategies and find that they work, the kinds of conditions that Christy was just talking about, and those can be, those strategies can be expanded to other conditions.

1:14:03
So, right now, there's a lot of interest in treating these kinds of conditions, which is great for people that have them.

1:14:10
And I think it also will yield treatment's beyond inherited neuropathy, eventually.

1:14:15
Well, that leaves us us here, and all our patients with a lot of hope. And we appreciate your time.

1:14:22
I think we could probably, have another session. And, and keep talking about this very interesting topic, but we appreciate your time, and your expertise, and appreciate everybody joining us today.

1:14:36
I want to just make mention that as a follow up, too, this presentation.

1:14:43
I wonder when would like to announce that we will be having a webinar next month?

1:14:50
Um, That will be, at the end of October, it will be based strictly on one condition that manifests itself, in peripheral neuropathy.

1:15:03
The HIE TTR EMEA Doses that will also be sponsored by El nylon and that will be will be on the 26th of October, which happens to be Global Global Justice Awareness Day. So that was a lucky break for us, look for our website, or our e-mails. We will be announcing registration for that soon, and then a final. thank you.

1:15:31
If you liked what you heard here, please continue to support us. You will get a recording seminar. us rather, a survey after this seminar that we'd love for you to fill out to give us some other ideas. And if there's anything else we can help you with, please contact us. And with that, again, thank you, and hope to see you all at our next webinar.

1:15:57
Have a good afternoon.