- Good morning, everyone. My name is Amy Gray and I'm the Chief Executive Officer of the CMTA. And we're just thrilled that you're here to join us for what we believe will be an incredibly informative, educational and engaging day. We have over 400 people registered for our conference today, people from all across the U.S. and around the world, internationally as far away as Australia, Egypt, and across Europe. So, welcome to all of our international guests as well. One of the aspects that makes these conferences so special is the opportunity to connect with fellow CMTers. And although we're not meeting in person or meeting virtually, our teams work really hard to make this as engaging and interactive as possible. So, we have some sessions planned where you can connect with one another over the breaks and over lunch. So, we really encourage you to participate in those. And we'll be giving directions on how to click through the links to join those activities as the day goes on. We have an absolutely incredible lineup of speakers for you today. And I want to thank each of our speakers for giving us their Saturday, but not just their Saturday because I think what we are so appreciative of is each of these speakers is so engaged all throughout the year in supporting our CMT community and our CMT patients. So, we want to thank them for the work that they do year round to support the CMT community and our mission. I also want to thank Laurel Richardson, our Director of Community Outreach for putting such an incredible agenda together today, incredible lineup of speakers. She's an absolutely amazing ambassador to the CMTA. And we have a number of staff online as well today that you'll get to meet throughout the day. Just an incredible team that's here to support you and help you and provide resources in your journey with CMT. The conferences, as you can imagine, are made possible through the support of individuals and corporations. And through that support, we're able to host activities. So, I want to thank our corporate sponsors today that made this possible, Pharmex, Cydan, Allard, Psychogenics and Stealth. Thank you for your support and your funding to make this conference possible today.

- Good morning. My name is Steve Scherer. I'm a adult neurologist at the University of Pennsylvania. Oops! It's not going to let me advance here. Wait a minute. And I'll be speaking first followed by Tanya Bardakjian, who is the genetics counselor who works with me at the University of Pennsylvania. And the goal of our presentation is to spend about 20 minutes apiece bringing you up to speed on CMT and then genetics of CMT. And then we're going to have 20 minutes for questions and answers if everything goes according to plan. So, I'm going to set a timer and I'm off to the races. So, I want to give everyone a chance to sort of get up to speed with the various names and terminologies and concepts that goes with the diagnosis and ultimately the treatment of CMT. And for someone who's been doing this for their whole adult career, I want to introduce you to the idea that people with CMT get seen by people like me, who care about the genetics of neuropathy and through a process that I'll describe in a moment, we come to discover that somebody has CMT. We do an investigation to find out if we can discover the cause of their CMT, which is to look at their DNA directly. And if we're able to find the cause of CMT in that person, then that actually opens a door to scientists to actually investigate why a mutation in a given gene causes neuropathy. And this is a huge step forward in our last 20 to 30 years that we've been able to figure out not only the gene defect but have

tools to investigate how that mutation causes neuropathy. And in so doing, we can actually make models of the disease in cells and even in rodents. And those models enable us to gauge what might work to fix a kind of CMT. And so, if that step goes forward and we just heard, or we will hear about CMT1 in the afternoon for the person on the call whose child was just diagnosed with it. If we have a model and we can make the model tell us about the basis of CMT and we can treat the model, then maybe we can even find a treatment that will work in people. And that's the goal, is to bring it back to the people with the CMT. So, this circle, I've been working on various aspects of this for my whole adult life. And I think we are on the verge if you hang around until this afternoon of actually having a way to go from here, this last step to a treatment in people. And so, this is an incredibly exciting time to be working in this field because when I started, we were just on this first era, we were just trying to find the genes 30 years ago. And here we are all the way to trying to make sure that the treatments work in people. So, CMT or Charcot-Marie-Tooth disease, it's just a name and all that's meant by this name when it's used properly is that it's a name for hereditary neuropathy of some kind. And there are many names like CMT that sort of you may have heard of, you may have been given a diagnosis of any of these different names on this list. But the names aren't the thing that matters the most. It's the idea you have a neuropathy and that there's a genetic cause of the neuropathy, and a name is what conditions give it to sort of simplify or make clearer to their colleagues when they're discussing a person with their hereditary neuropathy. So, there are many names for neuropathies, CMT is one, it's the commonest one, but it's not the only one. And all of these names, and at the end of the day, mean that you have a hereditary neuropathy of some kind. So, how do you figure out that somebody has a hereditary neuropathy? Well, first and foremost, if they seem to have a neuropathy when you examine them and we'll get to that in a minute, and it started early in their life, but especially if they have other people in their family who have the same thing, then you can be pretty sure from the get-go that that person and other members of their family have a hereditary neuropathy. So, one of the clues, in addition to the family history, because sometimes there isn't a family history is to know a couple of things about the CMT. So, if somebody's neuropathy began before the age of 20 to 30 and they have no other reason to have neuropathy that can be figured out from their medical history, then the suspicion that that neuropathy is inherited is very high. So, if you're talking about pediatric age group kids in the first 10 years of their life and they turn out to have an neuropathy, the vast majority of those kids are going to have a genetically caused neuropathy. And so, in some form or another, it's going to be a form of CMT. Now, we'll talk about how the nerve conductions help us discern two major types of CMT later in a minute. But even in this early age group, we're pretty sure it has to be CMT. Now, what's more problematic and maybe people on the call fall into this are people whose neuropathy say begins after the age of 25, or going up to the age of 50. And maybe they don't have a family history of neuropathy but no other cause of neuropathy can be found. Some of those people have hereditary neuropathy. Here are a list of genes that are found in people whose neuropathy begins after the age of 25. But we're much less able to figure out for individual people whose neuropathy begins as an adult what the cause of their neuropathy is. This is just... The field hasn't figured this out

yet. And so, we're sort of stuck in finding the causes of neuropathy for people whose onset is after the age of 30. So, two things that are listed on this slide. I want to go into some detail. One is how the clinical exam tells a neurologist that a person has neuropathy. And the other is how the electrophysiology or EMG clarifies the sort of the classification or the kind of neuropathy that happens to be. So, when you visit the neurologist, likely they use the reflex hammer, a tuning fork of some kind, this is just a fancy one, and a test of temperature and pinprick sensation. So, using these three tools and also just manually testing how strong somebody is you can determine whether or not motor weakness is present, and you can determine whether or not sensory loss is present. So, in most people with hereditary neuropathy and most people with neuropathy of any kind, it's the most, distal axons, the longest axons the ones that go to the feet that are affected first. So, the first change that many of you have experienced that if you can recall might've been sort of a sense of numbness in your feet or maybe it was a foot drop that your feet slapped when walking and somebody noticed it. And so, those are manifestations of neuropathy that happen to depend on the fact that the axons to your feet with the longest axons in your body. And when a neurologist examined you, then they also noted that you were weak in the muscles to your feet, that maybe there was also some loss of muscle mass that's called atrophy. And when they checked your ability to sense a tuning fork or the pinprick, they noticed that your sensation was less in your feet than it was say up your leg or in your thigh. Might've lost your reflexes at your ankles. So, all of that taken together says that you have neuropathy that affects motor and sensory nerve fibers. And the typical pattern is first in the feet and over time, extending up the legs and maybe even getting into the hands and arms. So, this is just a picture of somebody who has the axonal form of CMT and what the little red arrows point to is that there's atrophy of the intrinsic hand muscles. So, there's a little loss of muscle mass here in the thumb. And if you look at the hands over, you'd lose it there. So, that's the loss of muscle mass and you would expect that that muscle would be weak. And indeed it is. So, that's an obvious motor manifestation. This is a schematic that sort of indicates that I already said that neuropathy began in the feet but over time, it becomes more intensely numb in the feet. And even the numbness will ascend up the leg. So, I'm sure everybody on the call who has a sensory involvement recognizes this sort of picture of their neuropathy. It's worse in the feet, gets better up the legs and might even make it up to above the knees and in the hands, it's most intense in the fingers and might even extend into the forearm. So, this is just the manifestation of neuropathy getting worse over time and the sensory loss getting in a graded way worse in the distal extremities, and then even progressing up the arms or legs. So, I want to talk for a second about the nerve conductions because today and for the rest of the talks, you might hear the term CMT1 and CMT2 or demyelinating CMT and axonal CMT. So, these are inferences that are usually made by the fact that when you do a nerve conduction, if the conduction is normal, we'll say 50 meters a second in the arms that that's a kind of CMT where the axonal loss is the problem. Whereas people that have very slow conduction, say 20 meters a second, that's going to be a problem where there's a demyelinated neuropathy and axonal cell is a problem. And even some people have a sort of in-between numbers, and there are certain forms of CMT and CMTX is famous for this one. The nerve conductions are

actually right smack in the middle. So, it's a more complicated picture. So, this is one of the EMGs test arms that I like, what they did is they stimulate here at the wrist. We get this little motor axon potential over that muscle at the thumb, the one that was atrophied in the other slide. We stimulate it at the elbow, we get this upward deflection. We can measure the distance and we can use the distance divided by the time. And we can deduce how fast the conduction was. So, if the conduction is slow, then it will say 20 meters a second, then that's demyelinating CMT and if it's not slow, then that's probably an axonal CMT. So, to bring this all the way back into a picture is that CMT is when there's involvement of motor and sensory axons. There's basically 63 genes and 74 named disorders that fall into this picture where there's motor and sensory axonal deficits and then many genes and many different names for the diseases caused by mutations in those genes. A few people on the call may have one of these other conditions that are sort of right next door to what we call CMT. But it's really the same thing. It's whether the only motor axons are affected. There's no sensory involvement at all. That's often given the name hereditary motor neuropathy, HMN. And conversely, if only sensory axons are involved and no motor axons, then you're just talking about somebody with sensory loss and that's hereditary sensory neuropathy. And so, you can say that they obviously are a lot in common with CMT. It's just that some have purely sensory, some a purely motor, most people have both. So, now to the point where we can sort of start talking about the genes in particular. We've gone through the fact that if there's a history, especially a family history of neuropathy, other people are affected. There's an early onset under the age of 25 or 30. So, we're really thinking of CMT. We do an exam that validates there's a motor and sensory involvement in the arms and legs, the nerve conduction, either show want to talk about the old way. Many of you had single gene panels or single gene tests 10 and 20 years ago that cost a fortune. And now we're doing a completely different type to that. So, this slide sort of gives us summary of all of the people that we're seeing at one of the CMT centers of excellence, not only the United States, but also in Europe. There were some 2000 patients that were investigated to the cause of their CMT. And it turns out, and this will become a theme again and again, that the most common forms of CMT are this blue wedge of the pie. And that's the CMT1. That's the one with slowed conduction. And almost everybody in this slice of the pie has a disease called CMT1A, and we'll be talking again about that in the afternoon. This is the disease caused by a duplication of the gene PMP22. So, CMT1A is the vast majority of the people in this blue slice of the pie, which is the majority of people with CMT. So, one form of CMT1A is the most common form of CMT by a lot, half the people with CMT have it. It's therefore a focus of great interest in finding a therapy cause we sort of know what goes wrong there. And it also means that these other forms of CMT the ones that are physically identified are. Somebody has got to mute themselves. Leslie, you got to mute your microphone. These other forms are all rarer and therefore little known about them. And there's a considerable fraction of the pie where we don't even know the cause of the CMT. And most of these people are the adults who have an axonal CMT. And we simply don't know enough about the causes of adult axonal CMT to fill in this blanket. But one of the goals that we'll hear Dr. Zuchner speak to you in the afternoon is how to fill in this gap, how to make this pie complete. So, there's probably another hundred causes of CMT to be found. We already

know a hundred, but there's probably a hundred causes that fill in this blank. Now, what the CMTA has focused in on and for good reason are what's the commonest forms of CMT. So, I already told you, CMT1A is the most common. The second, third and fourth, most common forms are CMTX, 2A and 1B and so, most of our efforts are focused on finding the causes and the treatments for these commonest forms of CMT. What I have in parentheses here is actually something that's at least as common as CMT1A, HNPP, hereditary neuropathy with liability to pressure palsy, and you can see why we call it HNPP. This is sort of the mirror image of CMT1A. It's caused by the deletion of the gene PMP22. But it turns out that most people that have this neuropathy never see a neurologist, they never have enough symptomatic changes in sensory or motor function that they ever even think anything's wrong. And the majority of these patients are found almost by accident when they see a neurologist for something else. So, I think this is my last slide. And the bottom line here is is that CMT as you probably experienced and can tell me horror stories about is not a diagnosis that most neurologists can render efficiently when somebody shows up unless you show up already knowing that you have it. The CMT Association has made a considerable effort along with the MDA to invest effort into having people who know a lot about CMT, be called CMT Centers of Excellence. And we tried to represent as best we can the geography of the United States in this effort, such that if you get diagnosed and you want to see somebody who's particularly knowledgeable about it, you had have the opportunity if you're willing to make a road trip. And so, this an up-to-date image of what the Centers of Excellence happen to be , it's about 80% correct. But in any event, if you contact the CMTA, they will steer you towards a Center of Excellence that's near to you so that you can get the care that you're looking for and the information that you need. So, I finished almost a little early, so we have extra time for questions. And that will be handled at our talk. Thank you for coming to the meeting today. It's been my pleasure to speak to you. So, Tanya, I'll ask you to take over. I think maybe I click on stop sharing.

- Good morning, everyone. My name is Tanya Bardakjian. I work with Dr. Scherer at the University of Pennsylvania. I'm just going to take a moment to get my presentation up. Okay. All right. So, as we all know, genetics is a rapidly growing field. And as Dr. Scherer said, over the past 20 years, we have discovered that the growth in genetics has led us to know that genetics is actually playing a role in almost every area of medicine. What's important to realize is as we're discovering and answering a lot of questions, and the more questions we answer, the more questions we raise. So, I'm going to talk today to kind of give an overview of what is genetics, how does genetic testing work and what is the role of genetic testing within the CMT community. First, I want to go over just a couple of things where it's important to understand the difference between all of these words that you hear, with the diagnosis and the type of CMT. What we say is that there's a phenotype, and the phenotype is what is the clinical descriptions of the signs and the symptoms of a specific condition? And then the genome type is the actual genetic variant that is identified that causes the clinical symptoms. So, one important question that you would need answered is is your diagnosis or your family's diagnosis based on phenotype or a clinical exam, and a clinical diagnosis by a neurologist or a genotype? Which means have you

actually had a genetic test and received a report that tells you what is your genetic change or mutation that's causing your inherited neuropathy. As Dr. Scherer mentioned already, all CMTs are not the same. There's dozens of specific subtypes based on clinical and genetic differences. We do know the vast majority of these genetic causes but not all. And why it's important is that the natural history or what the disease can look like over time and potential treatment targets will be based on a large part on the specific genetic pathways, which is why it's important to try to identify the genotype for an individual if we can. So, a lot of people used to ask us, why ask why? What difference does it make? I have CMT. What difference does it make what the cause is? Well, for most genetic diagnosis, the answers are varied but they include, it can alleviate guilt and misconception. Some people think it was trauma or alcohol or whatever it may be. And it can really relieve a lot of guilt to say, "No, this was a genetic change that I was born with, even though my symptoms didn't appear until adulthood." That can give relief because it's an accurate diagnosis or it confirms the clinical diagnosis. We can better anticipate what will happen over time. What will your condition look like? Although we can't say for each individual what their course will be, we can say on a whole, an individual with CMT1A or a PMP22 duplication, which is the genetic cause of that. This is what it looks like over time. We can give accurate recurrence risk when we know the exact genetic cause. What does this mean for your children, for your siblings? It can help for access to clinical trials. You have to know your genetic mutation for some of these clinical trials and it can assist individuals in family planning. So, with different genes, you will find that there's different natural history, different inheritance patterns. And we think probably different treatments in the long run, depending on what the genetic cause is. So, now I'm going to take you back to kind of bio 101. Very simply, I'm going to explain what genes are and how they work. So, chromosomes are kind of like the bookshelves that store all of our genes. We have 23 pair or 46 total chromosomes. This is what they look like under a microscope in the cell, but we know how to match them in pairs. And this is important. They come in pairs because we get one from our mom and one from our dad. And then these are called the sex or gender chromosomes, two Xs results typically in a female, an X and a Y would be a male. So, to give you a schematic in the cell is the chromosome, on the chromosome or the genes. And the genes are made up of DNA. And the DNA have these four letters, A, C, G and T. We kind of say that the genome, the entirety of our genes is a book. Each chromosome is like a chapter. Each sentence is a gene and the letters are the DNA. The genes are like the instruction menu for our body. Each gene is like a recipe and needs to be spelled just so to make a certain protein. And the protein is the workhorse which has a very specific function in CMTs or in neuropathies, all of these genes somehow interact to make the nerve or the nerve muscle work appropriately. So, an abnormal recipe leads to an abnormal protein product, either too little, too much, or just an incorrectly formed protein. So, what are the bases? The most common DNA bases, there's four of them, A, T, C, and G. And they make up three letter words. Some changes are called mutations in a gene. And they're called mutations because it causes the gene to malfunction. But it's important to know here that some changes in our DNA are called benign polymorphisms. That means we have some changes that do not cause any sort of disease or symptoms. It is what makes us unique individuals. And the

difficulty in genetics is noting what is considered a mutation and what is just a normal polymorphism that makes each of us individually unique people. What's important is that none of us are perfect. All of us, regardless of our ethnic or religious background, carry six to eight genetic mutations that place us at risk for disease or to have offspring with disease. So, all of us have a mutation. The question is, does it result in a condition? I'm going to take you back now to what happens in a genetic mutation? Literally one letter change in our DNA base can change the way the entire gene works. And I think this sentence can show very well. Changing this one letter here, the H to a B changes the meaning of this sentence entirely. Instead of the gray cat ran down the hall, we have the gray cat ran down the ball. So, changes in DNA might change the way genes works, because it just doesn't make sense to the body anymore. So, before, like Dr. Scherer alluded, genetic testing was quite expensive. We didn't even know a lot of genes. We found one, then the other, then the other and genetic testing actually was done by a single gene approach. You would do one gene, thousands of dollars, weeks, and months of analysis. You would get a negative result. Then maybe you'd go to the next gene. About eight to 10 years ago, a revolutionary technology called panel on next generation sequencing came about where we can actually look at a whole bunch of genes that we put together on one gene panel because they have similar clinical picture. So, the inherited neuropathy gene panel is an example. We can massively parallel a sequence at the same time multiple genes that we know cause inherited neuropathies. This is cost-effective. We can test more than one gene at a time. Usually, more than 20. It's very useful when the phenotypes or the clinical exam overlap. So, in neuropathy, for example. And when I say it has good coverage of each gene on the panel, it means that if a gene is on this panel, that lab is promising us that that gene is looked at very closely and any variant, any change would be reported to us. What are possible results that you might get from doing this type of testing, the inherited neuropathy panel? And many of you might've had this done. So, there's three possible results when you're doing clinical genetic testing, positive, negative, uncertain. A positive means the cause of your clinical symptoms has been identified. Then a genetic counselor can sit down with you and say, "This is the cause. "This is what it means for your natural history. "This is what it means for your family members, "who is at risk, who is not at risk." A negative result does not mean you do not have an inherited neuropathy. A negative result means we did not find the cause of the neuropathy in you or in your family. And an uncertain result means we found a change in your DNA but we have no idea if this change causes symptoms or it might be a normal polymorphism seen in the population. Over time with a lot of research, we will clarify these uncertainties. And at a Center of Excellence, for example, we manage these uncertain results for a long time. We keep them in special databases. Dr. Scherer and I stay on top of the literature to see if these things are clarified over time, which we will come back to you and tell you. And then a brand new technology in the past several years has come out when panels don't give us an answer. And that is basically looking at the entire genome. We have about 20,000 genes. We only know what about 7,000 of them do. So, there's thousands of genes that although we know how they're spelled, we don't know what they might be doing to our body. So, we can't even analyze them clearly. A gene panel, like a neuropathy panel will look at about 70 genes only. You have thousands and

thousands of more. So, if that first test doesn't give us an answer, we do what's called reflect. We go on to look at the rest of the genes. And there's two tests that we can do. Clinically, meaning through insurance, the only thing available is what's called an exome. It will only look at what we call the active parts of our gene, the next best thing which is available only through research now is the genome. The genome looks at every single letter in our entire genome. It's a lot of data. It's very hard to interpret, and we're getting better at it, but it is not available through insurance, only through research avenues, which again a Center of Excellence would help with because we all are looking for new or novel causes of CMT or neuropathies. But it is like looking for a needle in a haystack. There are thousands and thousands of letters of DNA that need to be sorted through. So, really the genome becomes more of a research avenue that we're taking right now to find new causes of inherited neuropathies. And this brings me to a very important point. The difference between clinical versus research testing. A clinical genetic test is your neurologist and sometimes along with the genetic counselor will select the appropriate clinical tests. We start usually with the inherited neuropathy panel. We get the diagnosis, gives us the risk information, that paper with the results are given to your care doctor and to you. And it's kept in the patient's medical record. Clinical testing can come with a cost or through insurance. And I'll talk a little bit about that, but this means it is a test for which you are guaranteed a result. Yes, no, or maybe, but the result is given to you. But research test is very similar. We usually start looking at the very focused genes. Then we might go on to do whole exome or genome because we're looking for new causes that were not found on the initial test. This is often not kept in your medical record. It does not have a cost. It's usually paid for by the researcher. And it is kept in the researcher's records, but does not always guarantee that you will be informed of the results. And that's important to know. So, when you enroll in research some of the questions to ask are, will I ever be contacted? Will this information be given to me? And the answers are always different. So, it's important to understand the difference between is this test a clinical or research test? And what we often recommend is both together, because a clinical test if you find an answer, it's great. You know your answer, and you don't need to do more DNA testing often when you have the actual answer. So, what is a genetic counselor? And what do we do? The process of genetic counseling is to help people understand and adapt to the medical, psychological and familial implications of genetic contributions to a disease, any disease, in this case, inherited neuropathy. And the process integrates interpretation of the family medical history so that we can assess the chance of the disease occurrence or recurrence. It's to educate about inheritance, testing options, management about the condition, any potential prevention, resources and research to connect you to that. And then of course, counseling to promote informed choices and adaptation to the risk of that condition. Our job is not to give you our opinions but to make sure you're making choices and decisions about your care based on accurate information. So, who should have a genetic counseling appointment? And I tell people any individual or family who's concerned about a genetic disease may benefit from genetic consultation, regardless of whether genetic testing is available or even desired. Many people just seek information and coping strategies as much as test results. And genetic testing does not always mean... Genetic counseling

does not always mean genetic testing. Sometimes we see people just to help them adjust or adapt to their genetic test result that was ordered by another provider or to help interpret test results. Sometimes a neurologist or a primary care doctor will order a genetic test that they're not exactly sure how to interpret, and we can help with that. So, genetic counselors help translate. We help navigate and we help link you to support services in your community and for that specific condition. Now, what a lot of people ask me is, well, who's going to pay for this genetic testing? There are lots of ways to get clinical genetic testing paid for. There are specialty laboratories that do this testing and they really help get prior authorization for this kind of testing. Most insurance companies do cover genetic testing and most people pay less than a hundred dollars, with their copay and deductible. There are options such as sponsored testing. So, the MDA and some pharmaceutical companies do cover the cost of genetic testing because they want people who can benefit from their treatments that are being developed to have access to it. So, if there is an inherited, excuse me, neuropathy panel available from a laboratory at no cost to patients because the pharmaceutical company is paying for it. Medicare, Medicaid is covered for most of these if we get letters of medical necessity. So, it is entirely possible to get genetic testing clinically at no charge. So, working with the genetic counselor can help with informed consent. We can help navigate the complexities of genetic testing options, where they're well-versed at different offerings at different laboratories with insurance or the sponsored programs. And we can help ensure that the results are managed appropriately. A genetic test is useless if you don't understand that. And if it's not integrated into your medical records to help you and your neurologist care for your condition and to provide that information for the family. And with that, I will stop sharing my screen so that Dr. Scherer and I are available for any questions you might have.

- Thank you. Tanya, thank you so much, Dr. Scherer, thank you for excellent presentations this morning. We have a number of questions that have come through the chat function, and we'll ask guests that are joining us today to type in any additional questions that they have. And I'll just kind of start with the first questions that came through and we'll work our way through those. The first question that came up was when Dr. Scherer showed a map of the Centers of Excellence for the MDA and the CMT. And there was a red dot in Georgia, and a participant was wondering what site or center that was.

- I think that's a question for Amy or somebody from CMTA team. It's probably in Atlanta, Emory but I don't know for a fact.

- Okay. I can check with our call collaborators at the MDA. I believe it's one of the MDA sites and we'd be happy to get an answer to the the guest that asked that question today. The next question that came up was about X-linked CMT and how that's passed from the mother or the father. And just a further explanation on that.

- Okay. So, in X-linked conditions, if you remember a woman has two X chromosomes, a male would have an X and a Y. So typically, if the male is affected, that's a mutation on the X chromosome and they only have one X. So, a mutation causes the full-blown condition. An affected male will not

pass it on to his son because a father only passes on a Y to their son. So, a father cannot pass on X-linked CMT to their son, but all of his daughters will be a carrier. So, all of his daughters will inherit that mutation and be carriers. And carriers can have some mild symptoms. And then a female who's a carrier has a 50% chance of passing it on to her son to be fully affected.

- Thank you, Tanya. Another question came up about options patients have to not pass the gene on, and to break the words were used, how to break those cycles. So, could you talk a little bit more about that?

- Sure. There are several options that we would sit down and talk to families about. And of course, there's adoption. There's donation of either egg or sperm depending on who the affected individual are. There's prenatal testing if you know the cause, you must know the genetic cause in your family. And then there are options called PGT, which is pre-implantation genetic testing for monogenic or single gene disorders. And that would be using in vitro fertilization and genetic testing so that only embryos that don't have the mutation are then transferred into the female or the uterus for pregnancy. These are costly, both physically, financially, and require a lot of investment of time, emotion, but they're available. And any reproductive center that does in vitro fertilization can do this. But again, you must know the genetic cause in the family in order to have reproductive options available to you.

- And then the question came up whether it's known what the mechanism is that causes leg cramping.

- Steve, that's for you.

- That sounds like a me question. So, cramps as they're medically sort of defined are usually the problem of the nerve fibers in the muscle sort of becoming spontaneously active like them. Normally when your muscle moves, your nerve fibers are just sending a message to your body. But if a nerve fiber just has a flurry of electrical discharges, it's going to make the muscle to which it's attached contract very tightly which generates pain. Cramps are very common in CMT. And usually, it's in the feet first and later in the calves. They're incredibly difficult to treat. The best medicine that's ever been found for them isn't available anymore because it causes an effect on the blood cells that made the FDA take it off the market, but that was quinine. So, you can't get quinine anymore. But people are working on whether if something like quinine might help. It's been a problem for patients forever. And I myself haven't found anything to work consistently well.

- We had a question come in about, can children be genetically tested and then specifically for CMT2s?

- For Tanya.

- Yeah. Again, if you know the genetic mutation, yes. However, when we're talking about testing asymptomatic children, there's a little bit of controversy. So, I would say you need to think about whether or not you feel that child as they get a little bit older. We usually at least

recommend assent so that their child is at least 10, 11, 12 if they're asymptomatic to help make that decision, do they want to know? But technically speaking, yes, I would not do it outside of the context of genetic counseling to make sure that everybody understands the ramifications. Cause that would be considered a pre-existing condition if you test positive. If they're asymptomatic, if they don't have symptoms.

- Then we also had a question about getting evaluated or having a follow-up visits with a clinician out of state and how insurance deals with that.

- I'll take that one. So, if it's a genetics counseling thing, and Tanya will have to answer, but if it's just for a routine visit, I see people who come from New Jersey, Delaware, Maryland, New York in addition of Pennsylvania. And it's pretty rare that insurance companies don't allow for their patients to be seen. There's an exceptional issue with New Jersey when you're on Medicaid in New Jersey, they don't want you going out of state. So, if somebody has CMT, I just see them as a research patient because I'm the best neurologist for the State of New Jersey when it comes to CMT. So, I can't deny people who have CMT the access to seeing me. So, I just do it as a research visit and that's fine. It's not so many patients.

- Okay. And then here's a question for Dr. Scherer. How close are we to developing a treatment for CMT1s?

- So, you should come to the afternoon session because we go through where we're at in some detail. I can tell you that there's a good model. Well, so there's different kinds of CMT1, but if you were talking about 1A, there's a model of CMT1A in both a mouse and a rat and we were in a research project, the CMTA collaborated with a group, a company really, I understand, in San Diego and we actually found a treatment that works in the mouse or rat. But the problem is is that the toxicity wouldn't make it feasible at this point to do the same thing in humans. So, we do know what causes 1A, we do know what causes most of the CMT1s and we have strategies for approaching them. It's just a big... There was a lot of technical things to be overcome to make things safe enough to give to people. And that's where I think most of the concerns are right now, is can we do it safely? And if we can do some of the things, but can we do it safely enough? And so, go to the session this afternoon and ask the question again.

- One of the participants mentioned that they understand CMT affects the nerves and sometimes the muscles, does it affect the lungs?

- So, the lungs are a muscle that are moved by muscles. The main one is called the diaphragm and the nerve to the diaphragm is called the phrenic nerve. And so, when people have bad enough CMT, it's certainly possible that the function of the diaphragm and therefore the movement of air into the lungs can be affected. Really depends on the kind of CMT that you have how likely that's going to be. And the way that I handle it, and I'm pretty sure I speak to what most of my colleagues do is I send somebody where there's a question, even a concern about lung function. I send them to a lung specialist and have them be evaluated. So, you can do pulmonary

function tests which really measure the strength of the lungs as part of what they do. So, that's how you get direct evaluation of a lung function.

- If someone gets a positive genetic test for CMT can that affect their ability to get life insurance.

- So, if you already have the clinical diagnosis of CMT, no, it makes no difference. It's telling you why you developed the condition. We do talk about predictive testing. If you don't have symptoms yet for any genetic condition, we do caution. There's never been proven discrimination, but it doesn't typically cause early death. So, they're not asking that with life insurance, they're usually not asking those questions. They are asking about cancer and cardiac disease. But it would be in your medical records if you test positive for a gene and don't have symptoms, and life insurance will access your medical records. You sign a waiver when you apply for life insurance. If it's outside of your employer, any employer sponsored life insurance is not allowed to ask. So, if you sign a waiver to get your medical records, they're going to access anything in your medical records.

- Can anything be done about sharp stabbing pain? And then there was another question on just what options there are to alleviate pain.

- So, this is a huge question and beyond the scope of what we can accomplish in a video chat like this. But pain comes in many flavors, but if we're talking about neuropathy pain, neuropathic pain. Again, that's a pretty common feature of many kinds of CMT. For some kinds of CMT, it's almost characteristic. And the treatments are both pharmacological, that is medications, as well as non-pharmacological depending on things that you can do with exercise and stretching. So, it's a big discussion, not a little discussion. And yes, there are things that you can try, and yes, they work to some degree, getting rid of a hundred percent of the pain is probably not feasible, but getting it reduced by half or a third, that's usually the goal that can be gotten to.

- Are there different physical manifestations of CMT?

- So, I think the answer to the question is yes but I would say that the majority of manifestations are going to be shared between CMT patients, that distal sensory loss, that distal weakness that I talked about. There certainly are peculiar things that happen to people that I think are bit caused by their CMT that are common enough to sort of be expected. So, really that's sort of a discussion that has to happen between the CMT doctor and the CMT patient and to make a determination whether any particular issue is likely to be the CMT or it could it be something else.

- Can massage help?

- Only if my wife does it.

- Sorry, I had to get a joke in there somewhere.

- So, yes, for cramping and tight muscles and all those things of physical therapy including massage are excellent modalities as a physical therapist would call them. So, everybody on this call, everybody who has CMT, who doesn't have CMT needs an exercise program that includes stretching and strengthening and endurance. And part of that program includes, particularly for people with CMT, some active and passive stretching is just really going to help you.

- We've had a number of questions about different Centers of Excellence, where they're located, who the doctors are at those centers. So, I know we've shared the link here in the chat function and we'll also make that available afterward instead of going through all those individual questions today. There's a full listing on our website as well. Maybe we can put that link up again in the session. There was a question on how likely is our hip issues with CMT1A.

- So, hip issues, specifically dysplasia where the joint, the ball and socket of the hip joint don't form properly is a known complication of CMT1A. I think it can happen with other kinds of CMT too. It ideally would be recognized early enough that some physical therapy maneuvers would be used. But if it goes its natural course at some point, usually people with hip dysplasia need a hip replacement surgery in order to sort of alleviate the pain that that causes. While we're on the topic, same for scoliosis. Scoliosis is definitely a characteristic of certain kinds of CMT. CMT4C, one where it's almost always seen. CMT1A I'd say it's probably problematic in about 5% of patients where they might need surgery, to the point that they need surgery. But, I don't know. So, these are known orthopedic complications of CMT. So, we do ask and in a pediatric setting where you can actively hope to manage them and prevent their full manifestations of harm or look for it and treat it.

- If a patient has CMT1B, what are the chances? Is it a 50% chance they will pass that onto a child?

- It's the genome.

- Thanks, Tanya. Yes, it's dominant. It's dominant.

- Okay. So, 50%.

- Okay.

- We also have someone that asked a question whether CMT affects the femoral nerve.

- So, the femoral nerve is the nerve that goes to your quadricep muscles. So, when you are sitting in a chair and you straighten your leg out against... Make your leg go straight, that's the quadriceps activation. Yes. The nerve, it's the femoral nerve. And it would be affected. But clinical weakness from CMT to the femoral nerve would only be happening in somebody with very severe CMT. So, almost everybody I see there's no weakness in the quadriceps. So, that would be very uncommon. So, if that were, especially if it was on one side and not the other, I would be looking for another cause of that weakness.

- Tanya, what advice do have for patients if there's siblings, one has tested positive for the... In this case, CMT2P, the other sibling's test came back inconclusive. So, what advice would you have in those scenarios?

- My answer would be like likely a different laboratory was used. So, the variant was interpreted differently. So, if they are working with the Center of Excellence or genetic counselor, we'd be happy to look at that. That would be my guess, is that it's the same variant but interpreted differently by the laboratory as pathogenic, which means disease causing or inconclusive. And that is possible because each lab has different experts working with them. But without more information, that's really all I can say. Steve, do you have any other input on that?

- No, I think that's probably the answer.

- Yeah.

- And then we have another question. If someone's been diagnosed with a PMP22 mutation but testing has not confirmed CMT1A, how common is this? And I guess what advice would you have?

- So, a mutation, we talked about CMT1A, that's the duplication of the whole gene. And then there can be as time you had that example of a single letter change where a cat became bat. I think that was it, but like if I remember. So, if it's that kind of a change, it's a different kind of mutation. There are some variants that don't cause disease. So, there are mutations that change cat to bat and PMP22 that have no consequence whatsoever. They're also prevalent in the population of people so that you find them more often than you would expect by chance for a disease-causing mutation. So, I suspect that's what's going on. There are known benign variants in PMP22. But without having the specific variant, I don't want to say more because that's where the rubber hits the road.

- Okay. And then we have a question about whole exome sequencing, testing was done and six CMT related genes were identified as variants of unknown clinical significance. Can someone in a case like this still have CMT without a definitive diagnosis, genetic diagnosis?

- Yes. The diagnosis is based on a good neurologist clinical exam electrophysiology. So, the genetic testing is trying to figure out why you have CMT, but CMT is based on a clinical diagnosis.

- And then we have another question. Maybe you can speak to this in generality, but if you acquire another condition, how can that exacerbate your CMT or are there other conditions known to exacerbate CMT?

- So, and I saw another in the chat as I was doing it. So, the famous thing that can complicate CMT would be chemotherapy that contains vincristine. If you have CMT1, 1A, 1B and probably even some other kinds and you get vincristine, that can accelerate your disease and can make you much worse. And so, for that reason, if somebody has CMT1A and their

oncologist wants to give them vincristine, I've always advised against it. I say, find another plan because we know that's going to be a bad thing. If it's other conditions, the only common condition that I could think of besides chemotherapy would be diabetes. People that have CMT of any kind who also have diabetes, diabetes causes neuropathy. So, it's sort of one plus one equals two. They have two things driving their neuropathy. And so, people with diabetes typically get worse with their CMT.

- Okay. I think we have time for a couple more questions and I just want to let everybody know that any questions that we don't get to during this live chat, we will respond, we can follow up with you directly. We have a question about automatic muscle twitching and how it can be treated or managed.

- I'm going to pass on that. I don't understand the question. Automatic muscle twitching isn't a concept I know.

- Okay. Do you know if ketamine treatments help CMT pain?

- I'm not familiar with any evidence that ketamine treatments help neuropathy pain.

- And then there's also a question about medical marijuana and if that can help with CMT pain.

- So, there are individual patients who have said that it helped their pain to some degree. So, I won't dispute that it can. As far as I know, there are no well-controlled studies looking at this in a systematic way that would make me have a strong opinion for or against medical marijuana in the treatment of pain. Until it gets studied properly, I don't think we're going to have a real answer.

- Yeah. And then what affect can CMT have on the eyes?

- So, I saw that question in the chat. There is a couple of kinds of CMT that do affect the retina. So, the eye thinning, the retinal thinning that you can measure with a special device is characteristic of CMT2A. Some mutations of CMT2A cause this condition in particular. The common forms of CMT like 1A, it does not. So, really gets down to the specific kind of CMT that one has as to whether that is a known association or not a real association.

- All right. And I think our last question will be, can someone have more than one mutation causing them to have more than one type of CMT?

- Yes.

- It is possible.

- There are probably 20 papers describing individuals where that's happened. You don't get to pick your parents.

- All right. And we have a number of other questions but I think we have a hard stop now. So, we'll make note of those additional questions in the chat function and follow up with everyone directly on those after the conference. So, thank you, again, Dr. Scherer. Thank you, Tanya, for your time this morning, incredible presentation, and for all the great questions from the audience today.