

- It's my great pleasure to introduce Gilles Bouchard. In addition to being a champion and patient advocate, he leads our board of directors. So I welcome to you Gilles. Thank you for all of the energy you pour into the mission for the CMTA. Thanks for being here today.

- Thank you all. Thanks everybody. I assume you can see my slide now in the background and you can see me speaking.

- Yep, perfect.

- Good, we're ready to rock and roll. So we're going to spend an hour and 40 minutes with the Q and A at the end. There's just more and more happening all the time with STAR. So we've really changed the way we approach this update from last year to try to cover more of the material. And also this time, and this year I'm extremely honored. We have four of our researchers who are going to help me and show us and share the STAR updates. And the first thing I want to do is give them a couple of minutes to introduce themselves. This way we'll make sure they're on board before we go any further. So first I'm going to turn over to Dr. Svaren.

- Hello everyone. I'm John Svaren at the University of Wisconsin. I serve as a chair of the Scientific Advisory Board for the CMTA.

- About Dr. Kleopa.

- Good afternoon, everybody. Nice to connect with you. My name is Kleopas Kleopa. I'm a neurologist and I'm in Cyprus. I work with gene therapy for CMT for different CMT types and also take care of CMT patients,

- Dr. Scherer.

- Hi, Steve Scherer, University of Pennsylvania. I work for you.

- And Dr. Züchner.

- Hello, pretty nice to meet you over soon. I work at the University of Miami. I trained in Germany as a neurologist and a geneticist, and I'm really striving hard to find the remaining genetic causes for CMT.

- Thanks, Stefan. So let's go a bit over the agenda for this update. There's really three major parts. First, for the first about a half an hour, we'll be all together in this one room and we'll go over the overall overview of the STAR program. The approach and strategy, and they are five areas of research, which tend to cut across all CMT. So all four doctors will explain a little bit what those are before we get into more details. About half an hour through, we'll break into two rooms. If you stay on this room, we'll talk about what we call demyelinating CMTs, which is type 1, type 4, type X, and Dr. Svaren and the Dr. Kleopa will cover this. And then we have another chat room about axonal CMT, so type 2s, and Dr. Scherer and Dr. Züchner will cover this. And this will take about 35 minutes and then we'll come back together, do some wrap up and then do a Q and A with the team. And while we are presenting, the chatroom will be open for questions and our team will collect those

questions and carry those to the team at the end of the session. All right, so let's get started. And first and foremost, we all have a reason why we're here today. And the reason for me, well he's right behind me, is that little guy here, my son Yohan was diagnosed with CMT more than 15, 17 years ago. He got CMT1A and that's how our CMT journey started, and I'm sure everybody's got their own story. So, and the reason why I put this pictures behind me is that for the first time this year, we started biking together when he go to an e-bike and that's been a life changer. So that's been really exciting for us. So that's, my first start to explain what the STAR program is. STAR means Strategy To Accelerate Research. It was started about 11 years ago when the board got together. And that's when even for myself, I was starting to get involved with the CMTA. And to be honest, it was depressing to look at the CMT world, because there were some great researchers working on CMT, but there was actually zero pharma companies working on it there was very little translational effort happening. So it was a bit overwhelming to figure out how do we move the ball forward? How do we find solutions for the community? And we got together and really took a very strategic approach. How do we solve the problem? Just the way we do it in a business. And the first thing you do in a business is to analyze what challenges you have and then how are you going to overcome those challenges? And there are basically, there were at the time and it's still true today, three major challenges we have to overcome through CMT. One is very generic, but that developing drugs takes a lot of time, in general well over 10 years. It takes a lot of money, often over a billion dollars and it is very risky. A lot of studies that show that over 90% of the drugs that enter clinical trials fail. So it's a very expensive, very slow, very risky business. And in CMT it's even riskier for companies to work because there hasn't been a successful clinical trial. There is no treatment. So the risk is viewed as being really high as well, and even higher. And then CMT is perceived to be a slow and progressive disease, which means it takes a long time, a lot of patients to run a clinical trial. So clinical trials are perceived to be slow and expensive. And that's also what was keeping a lot of players on the fence here. And these are still fairly true today, but we've done a lot of work to address those and that's what we'll be talking about today. Now on the plus side, there are some really exciting opportunities that CMT presents. And let me highlight a few. The first one, which we hear all the time now, especially that more players are coming to the field, is that the genetics are very clean now. So they're very well understood. There's a very clear relationship between a certain genetic effect and the condition of the patients. And believe it or not, this is very rare in the medical world and very rare in the world of nervous system diseases. And that's why you'll see a lot of our strategy from day one was to say, well, we know the cause of the disease so we can replicate it. And we created this very thorough and extensive testing environment with assays, which are already in vitro tests, tests in Petri dishes, STEM cells, animal models that replicate the disease. And as is often said, when you can replicate a problem, it's halfway solved. And that's been at the heart of the strategy and at the heart of everything you've heard about today. And then the other advantage, which has become really obvious the last two, three years has been an amazing amount of development, innovation and breakthroughs in the world of genetic therapies. And you've heard of CRISPR and gene therapy, on and on, and all of those elements really apply to CMT. And again, you'll see

amazing examples of that today. So that's what we focused on. The other interesting aspect is what's called biomarkers, and you're hearing a lot of biomarkers, but those are elements, whether it be in the blood in your skin, in your muscles, that become early indicators of disease progression. And we've done a lot of work on this and you'll hear a lot about it today. And we got to the point that we can conduct clinical trials and get much faster readouts on what's happening. And so it's a really important part of attracting more players into the world of CMT. And then the last time, which is more on the business side is CMT is a rare disease and is classified as such, and that brings a lot of advantages to companies, thanks to some acts of Congress. But also while it's rare, it's not that rare. So this was fairly large population which makes it a lot easier when you plan to conduct clinical trials. It's another big asset and we'll talk more about. So based on that, the core strategy for STAR from day one was how do you attract partners to work on CMT? Because we cannot do it at all. We don't have the billions of dollars that it takes to develop the drugs. So we need to attract top players, top labs, top technologies to CMT. So everything you've done for the last 10 years, everything you've heard about today's based on that. And I want to highlight basically five things that we found are important to attract partners. Not all partners want all five things, but a few of them are always important to attract partners. The first one, and you're going to get a great example of this today is experts, what they call KOL, Key Opinion Leaders, and you have four of them on the panel. And by the way, the four people are going to hear from today are very engaged with many of our partners on a daily basis. And the second one is this testing infrastructure. What companies want to do is they want to be able to test quickly, inexpensively and reliably their product and CMT models. And again, you'll see how much work we've done on this to create this preclinical testing infrastructure. The third one, we mentioned it already. They want a clinical trial infrastructure. They want disease to be clinical trial ready with patients, with natural history, with biomarkers and you'll hear a lot about what we've done in this area so far and where are we at. And then what's very interesting is, historically, most of the partners that were coming to us was because they had drugs, they had technologies that they wanted to try on CMT using infrastructure. More and more when we get a call from a player is they're asking, what do you have in your portfolio that I can take to the market? So more and more companies are looking for innovation that they can license and take to market. And you'll hear great examples of this today. And this is a very promising, and it's in all of the investment we made over the years, in the labs, in new developments now are starting to get a lot of interest from pharma companies. And the last one, which is very important, basically a lot of what you heard all day today is they want access to the community. They want to understand how CMT affects you, the patients. And that's why we've also developing all of those great elements to reach out to the community that you heard about today. So those are the five things and everything you've heard about today is about those five things. Now, the next question you ask yourself, how's that working? We've been at it for 10 years. So what is working? So let me show you a few numbers. On the expert side, we have an amazing expert advisory board. Again, you'll see for yourself the next hour when the people are speaking and we have over 30 advisors now, and they're very engaged with our partners. We've invested over \$17 million now and

counting in developing this infrastructure you see on the left in all of those areas. The first one being this testing infrastructure that I've described, and now we have research tools for all the major types of CMT because we keep adding to them every year. And what's interesting is a proof point this year alone, that we have 19 joint preclinical studies with partners that are using this infrastructure. Three years ago there was almost nobody using it. We were still building it. So when you can see we built this amazing testing machine and it's being used, which is the most wonderful thing we can think about because we'll see in our portfolio, lots of companies now are coming to work with us on CMT. And then in creating this innovation, we have over 50 active projects. And by the way, even though this year is a tough year with the pandemic, we've actually just approved eight new projects in the last couple of months. So we've been very active in again, creating innovation and building this infrastructure. We've been adding partners. I mean, again, when we started STAR, there were no partners. Four or five years ago, we had maybe a handful. Now we have over 30 partners as part of the STAR alliance and new people coming all the time, and knocking the door. We have like 12 active discussions now with partners. And again, you'll see some of those examples throughout the presentations today. And then in terms of infrastructure, working together with the INC, we have 35 centers of excellence. Many of you I'm sure have visited them. They're good for their patients. There's a lot of research going on there. They lead a big part of this clinical awareness and preparation and readiness that we have to put in place. We have branches, and you'll hear a lot of those things by the community, between the social media and the camps and all this. And so our community engagement is really reactive as well and you've heard about this all day. Another way to see how STAR is working is what we do call our pipeline, our portfolio. And this is a very busy slide, and I'm not going to go to details, but you hear a lot about a lot of those elements today. But this year we decided to put everything we're doing with all partners in one page. And the reason why this is a great way to visualize our progress in a way you can see how many partners are engaged. You can see also the breadth of technologies that are engaged, the breadth even geographically, there's partners around the world. And also you can see how far along they are on the timeline. And by the way, this is what shows us that we've made great progress because when we started STAR, there was one line on this chart. Three years ago, there was maybe seven to 10 lines. And now it barely fits on one page and we keep adding to it. But you also see a lot of those projects are what's called a preclinical stage. And the reason why it's important to have so many, because it's such a high risk business, we know if things move to the right, many are not going to work. So we cannot put our eggs in one basket and just spend on one thing. So now we have 50 things and we know that few of them will move to the right, but we got to keep moving in more and more things to the right and to add things on the left. And the last thing I want to point out is something we realized just recently, is this also really amazing asset that there are many types of CMT, because we tend to play matchmaker. Now, when a partner comes to us, we try to find a class of CMT that works the best for them that would make the most successful. Because it's such a high risk business, we really want to limit the risk for our partners. And you'll see throughout the presentation today that certain technology tend to be best first tried on some types of CMT on how it works and if it works then it will spread

across all CMTs. So this portfolio approach and this match making is really important. It's turned out to be very successful for us. All right, before turning over to the doctors, I want to highlight that first, we're going to cover those five areas of CMT and investment that cut across all CMT before we go into breakout. So the first one I talked already about is all this preclinical model. The structure and infrastructure. We're not going to talk more about it, but you'd basically be behind everything you hear. The footprint of this will be everywhere in what you hear about today. Then Dr. Kleopa will give you an overview of gene therapy and then we'll do a lot of details in both breakouts. Same thing for biomarkers with Dr. Svaren. Dr. Züchner will explain the importance of gene discovery and then, Dr. Scherer will explain a new area and it's really exciting for CMT called axon degeneration. All right. So I'm done from my part, and I'm going to turn it over to Dr. Scherer. So Steve, the floor is yours. Unmuted.

- So someone's going to advance a slide for me. Hi, good morning, good afternoon, good evening, wherever you are. Thanks for joining us today. I just have a few slides to present right now, and this is to sort of get us ready for the biology of what we have to do to fix CMT. So I'm reminding you that nerves are collections of hundreds, if not thousands of nerve fibers. And the yellow axon in the panel here surrounded by its chocolate myelin sheath is exactly one of these nerve fibers. It's a myelinated nerve fiber. And if you look in this other image next to it, you can see that there are many, many, many axons of actually different sizes that comprise a nerve. And the way I would have you think about this is that just like in this cable to the right, there are many different kinds of wires of different sizes. Well, nerves contain axons of different sizes that do different things. Some are sensory nerve fibers, and some are motor nerve fibers, but at the end of the day, neuropathy affects one or both kinds of axons and that's why we have problems. Two different cells are in this picture. The cell that forms this myelin sheath is the Schwann cell and not pictured in this image is the nerve cell body that gives rise to this axon. So if we could go to the next slide. Thank you. So this is the cartoon of what I just said. Here is a nerve cell body on the left-hand side of the panel. It has its long axon that goes down to where it ends. And all along the length of the axon we see these individual cylinders that are the myelin sheaths that I showed you in the last slide. And there's a small space between each of these cylinders. Those are the nodes of Ranvier and electrical impulses travel from node to node to node. And that conduction is ever so fast 80 times faster the conduction is with the myelin sheaths than without it. And so myelin is a fundamental and important adaptation of nerve fibers so that they conduct things quickly. What matters to us here today is that there are many different mutations, some of which affect the Schwann cells that make these myelin sheaths, others of which affect the nerve cell bodies that make the axon that goes down the nerve. So if the mutations affect the Schwann cell, inevitably the result of that is demyelination. And so there are gaps in the myelin or there're gaps where there are no myelin sheaths. Conduction has slowed way, way, way down and furthermore, without the protection of the myelin sheath, axons over time, even in demyelinated neuropathies tend to degenerate. So the problem for demyelinating diseases is a Schwann cell problem fundamentally. Fixing the Schwann cell is what we're always trying to do.

And if we can, we'd also recognize that axonal loss that's superimposed on this problem is something that we would like to prevent. In the case of the axonal neuropathies, the defect is playing out in the nerve cell body of the neuron, and somehow that results in the degeneration of the axon, which is set some distance away, even like three feet away from the nerve cell body is the end of the axon. And so a problem in the nerve cell body at the end of the day, results in the degeneration of the distal axon. So fixing the nerve cell body so that the axons don't degenerate is the fundamental game to be played. Now, there are about a hundred different mutations that we know of that cause CMT in one of these two mechanisms. So either causing a Schwann cell problem, that's about 15 of the known causes, or cause a neuron and therefore an axon problem, and that's the other 85 causes that we know the name of. Fundamentally we want to know what we're trying fix. So if we're trying to fix the nerve cell body or are we trying to fix the Schwann cell. And if you join one or the other breakout problems, in one case, you'll be seeing us focused on fixing the Schwann cells, that's the demyelinating session for CMT type 1 and type 4. And then the session I'll be a part of, it's a neuronal problem or CMT type 2, and we're trying to fix the neuron so that axons don't degenerate. And the other concept that I want to plant in your head now, and I'm going to pick up on later in the session on axon problems is that there are fundamentally two different kinds of mutations. Some mutations are the result of a mutation in both copies of the gene, loss of function. There isn't any of the gene product being made by the cell and that's a bad thing. In the dominant mutations, one copy of the gene is actually quite normal and the other copy has a problem, but the one abnormal copy of the gene screws things up just by itself. And in those cases, it's a little bit trickier to think about how we fix that kind of a dominant problem. But if you go into the talks, you'll see how that has been approached both for the demyelinating forms of CMT, but also for the axonal forms. Next slide. And so the last topic which fits to all forms of CMT is an interesting discovery that there are genes that are required for axons to degenerate. And the most famous among these genes is called SARM1. And if you delete the SARM1 gene, axons don't degenerate at all in the same way they do as a normal. They're very delayed by weeks at a time. And so the belief is that if deleting SARM1 leads to that axonal preservation and people can now develop compounds that mimic that effect, that block the SARM1's enzymatic activity that degrades NAD, that's a protein or a chemical in the body, then you might have a means for treating neuropathies of many kinds, including CMT. So I've been involved as a full disclosure with a company called SARM that's trying to develop drugs like this, which was just sold to Lilly for quite a fantastic amount of money. Other companies are doing the same thing with also a fantastic amount of money backing them up. There are other genes in the pathway that SARM1 belongs to. And so some of these genes also could be targets of therapy. So we have to hope in the CMTA world that we will find drugs that block some one activity, and that at least for some forms of CMT, these drugs will prove to be therapeutic and prevent axonal degeneration. So it's a very, very big deal that this pathway has been discovered, and it turns out in the world of pharmacology to be druggable. What you can do to sort of show whether this is a logical target is the knockout for the SARM1 gene's conveyed by both in the mouse and the rat, and so you can breed your favorite CMT animal model to the SARM1 knockout and see of axons are

preserved, which would give you some hope for drugging those the SARM1 protein in people who have the same mutations. I think that's my last slide.

- Yes, so I will take up from here. Thank you, Steve. And you will hear a lot about gene therapy in the following slides. So we have a small introduction now about gene therapy. And if we could go one slide back, please. So, first of all, what is gene therapy? When we talk about gene therapy, we describe the use of genetic therapies to treat diseases. Please go one slide forward. And so this process involves the introduction of genetic material in the form of DNA or RNA, which is the messenger nucleotide of DNA in cells and tissues of an individual. Instead, for example, of treating a disease with drugs or surgery. And so the basic principle of gene therapy includes various methods depending on the cause of the disease. So if we have a disease with a mutation causing loss of function of the gene, so the gene is faulty and non-functional, then we use gene replacement. We introduce a healthy copy of the same gene into the cell. In the case of genes that have become toxic or they are produced in excessive amounts, then we try to inactivate or silence the gene. And in the cases of other toxic gene effects, we use gene editing, which is shown on the diagram on the right. So it's like cut and paste approach. We try to cut the portion of the gene that has the mutation and replace it with a healthy copy of it using very special guiding molecules. So if we go to the next slide, how do we deliver gene therapy? So in the next slide, you can see that most of the time we really use viruses to deliver the genetic therapies to the cells. And you can see the example here of what we call a vector, which is a modified virus. You hear a lot about viruses these days. So these vectors used for gene therapy have been modified. The genes that allow them to be infectious and to propagate have been removed, and essentially they are reduced to the capsid, the packaging part of the virus, and we can insert the genes we want to deliver into the virus DNA. And so the virus is used as a vehicle. It can enter the cells and once inside the cells of the body, it can release the genetic material, which goes to the nucleus of the cell. And then it can allow the production for example, of the product that is missing from the cell and therefore restore the problem that causes the disease. In the next slide, Can we go to the next slide, please? We now come to the ways we can apply potential gene therapies to CMT neuropathies and to CMT patients. So this is the same diagram that Dr. Scherer has shown before. So here we have to really tailor the gene therapies to the cause of the disease in order to address the disease mechanisms. So for CMT neuropathies that are caused by loss of function, which is mostly the case in the CMT4s and in CMT1X, we have to deliver the healthy gene to replace the mutated gene to restore function. For CMT neuropathies with a toxic gain of function, which is mostly the case with CMT1s and 2s, we have to try either to silence, reduce the amount of the toxic gene, or try to repair - edit the mutated part. In addition, we have target our therapies to the affected cell type and as Dr. Scherer explained demyelinating neuropathies are caused by mutations in Schwann cells. So in order to treat them, we have to deliver the therapies to the Schwann cells whereas axonal neuropathies are caused mostly by genes that are important for neurons and their axons. So in that case, we have to deliver the genetic therapies to the neurons themselves. And that's of course a requirement in order to achieve a therapeutic benefit for each

type of neuropathy. In the next slide you will see that there has been already a great development in the field of gene therapy for CMT neuropathies, and that's really a development that we see in the last few years. It has been encouraged by success stories in other neuromuscular diseases. For example, we have seen the gene therapy coming to clinical application for the spinal muscular atrophy. And so this has encouraged a lot of work for gene therapy, also in CMT. And the CMT association has really developed a comprehensive gene therapy support program which covers the major types and the majority of CMTs as you can see here in this diagram. If you click, you will see on the diagram how many types are already addressed with gene therapy efforts. So CMT association already funds work to develop gene therapy for CMT1A, 1X and 2A, the three most common types, but also for more rare types, such as 4C, and more recently 2E, 2F and 4A. And in this comprehensive gene therapy project, all different technologies that are applied for gene therapy are really used, including the use of viral vectors for gene replacement, for gene silencing, for genome editing with CRISPR CAS, and also using the antisense oligonucleotides to reduce the gene expression levels for the most common type, the CMT1A. And we will have more about this in the breakout sessions. So please stay with us. Thank you, and I will give over to John.

- Those of you who stay for the CMT1 and 4 session, we'll really see some spectacular examples that Dr. Kleopa and his work group has been working on. But even if he develops completely effective therapy, one of the limitations that we have is really having a good way to measure the neuropathy and to really measure a positive response to treatment. And so we've also invested in parallel to these different kinds of therapies into biomarkers. And many of you may be aware of these neuropathy scores that have been employed throughout the clinical network to help evaluate patients. And this is now extended to development of pediatric and infant neuropathy assessments. But since CMT is a slowly progressive disease, these neuropathy scores by themselves are not that sensitive to changes and therefore not really adequate to serve in a clinical trial as a measure of whether the neuropathy has improved. And then therefore it's been really critical for us to develop biomarkers for clinical trials because companies that want to invest in a therapy for CMT, they really demand that we have some measures that we can use to evaluate whether there's any signs of success, ideally within a three to six months of starting the clinical trial because a year or two years is really too long for them to make that investment. So we've been really trying to support development of biomarkers for this effort. On the next slide you'll see one example of a biomarker. This was actually developed by an outstanding CMT neurologist in London, Mary Riley, in collaboration with some MRI experts and what they've developed is a way to use calf muscle MRI as a very, very sensitive measure of CMT progression. What you can see in the left side here is the cross-section of a calf muscle. The dark material is the muscle itself and the white around the edge is adipose tissue and skin. And what they found is that as CMT progresses you get a gradual replacement of some of the muscle in the calf with adipose tissue. And in fact, the color coded version, which you see a little bit to the right here, is they've color coded all the different muscle components. And through a very sophisticated analysis program, they've realized that this actually can be used as a very sensitive measure of

CMT progression and as such in combination with other things it's actually going to decrease the number of patients that are required to power a clinical trial. It'll thereby decrease the cost of that clinical trial, thereby lowering the bar for companies to jump in and try things and will ultimately provide faster results. So this, along with some other biomarker efforts that we'll talk about a little bit later on are really vital to the success of bringing CMT therapies to clinical trial. I'll turn it over, I believe to Stefan.

- Thank you, John. So this is just a real brief introduction to CMT genetics. First of all, as you have heard CMT by definition is a genetic disease. So to really understand it, to develop therapies you need to understand the genetic basis especially when it comes to genetic therapies like Kleopas showed us. You just have to know what your gene is, if you are a CMT patient to benefit from this. And this is also true for other efforts in the pharma industry today. Even if it's not a single gene that caused a disorder it's probably no serious pharma effort anywhere anymore if you don't understand the genetic if you don't understand the mechanism of a new track down to a genetic mechanism. So that means some, you really have to strive to give as many CMT patients as possible an answer. And answer for me as a geneticist is to be able to tell a patient, every patient this is the gene that has a defect in you and your family. And then therefore you can give those options available. Now, for the demyelinating types of CMT, the CMT type 1 more than 90% of patients today receive this kind of answer if they do a clinical genetic test. For the CMT2 is these axonal types, it's less than 50%. And some studies even suggest it's a lot less than 50% of CMT2 patients can receive this answer today. Why there's such a gap still we sometimes called a C diagnostic gap is really, it's still a matter of debate. One thing is very clear. There are still a lot of novel genes to be discovered in the human genome that we simply don't know about today, despite all the efforts we have done. And you see in this graph here, this is roughly the last decade of CMT gene discovery really globally, published papers, published genes. So it's only on the low bar. The abbreviation still have the many smaller abbreviations. These are all single genes. And so you can simply see there are a lot of novel CMT genes that have been discovered last eight years that we didn't know about them say 10 years ago. We simply didn't know about them. Now we know about them. So now we can study them deeper. We can think about therapies. And in red, you see actually the CMT genes that have been discovered by the INC, the Inherited Neuropathy Consortium and the support of the Genesis project. So this is really something that the CMTA has supported in the past and keeps supporting this effort as it continues. And there will definitely be more genes being discovered. So no genome, it's very hard to develop a therapy, probably impossible. The other side of it, as many of you know, if you don't know your gene and you may have already undergone genetic testing, you often continue on what's sometimes called a diagnostic Odyssey. There is this lingering doubt that maybe you suffer from another disease. Maybe it's not even CMT. It's something else or simply you really want to know because you want to benefit and interact more with the projects that the CMTA may support with their partners to find a solution for specific types of CMT. So there are over a hundred different types of CMT today, just to give you an idea here. And so as you can see the future's bright. We have a

lot of work to do, but we've made progress finding more genes. There are other genetic projects that are ongoing, including in recent years, a focus on something that's called the modifier genes. Modifier genes, what are those? It's long been observed by physicians that in single families, even that carry the same gene and the same mutation, that there can be quite a difference between the onset of CMT in a father, and then the onset of CMT may be much earlier or much later in the children. So there are these differences and some of these differences are clearly environment in the wider sense. But some of these differences seem to also be because of other genes sort of secondary genes, or these so-called modifier genes. And it's also a major effort ongoing, supported by the INC. Also at the Jackson laboratory, there have been some phenomenal results recently in this area. And why would it be important to find modifier genes? The idea is, and there are examples in medicine now, sometimes it's easier to influence this modifier genes to have a better outcome. In some sense, the SARM gene that Dr. Scherer talked about, if we could therapeutically influence the SARM gene, that is sort of a little bit along the lines of influencing a modifier gene, or a gene and a pathway. So that's ongoing. Another big topic of course is these so-called variants of unknown significance. Now, it gets a little technical here, but some of you I'm sure have seen this on their reports their genetic reports that they have done a genetic panel and then the doctor says, well, we found one or two genes here. There are variants in those genes. We just can't be sure to call them mutations. We can't be sure. So we call those the variants, the genetic variation of unknown significance, uncertain significance. And that is not a good situation because frankly these variants, sometimes it can be completely normal and benign just by chance, and in other cases, they are the true mutation underlying in a patient. And it's been very difficult to work out which variants are benign, cause no harm, and which variants are actually really bad for you. So that's another field which is important because it really is very unsatisfying to do a genetic test and then get just variants back where even the best experts in the world cannot tell with certainty what they actually mean. And maybe one more word, just quite recently six months ago at the beginning of the COVID crisis, we had a major success, that is us researchers in a genetic and the CMT field in general. We published discovered a new gene, which is called SORD, S-O-R-D. And so we call it SORD neuropathy, doesn't have a number maybe never will. But this SORD gene seems to be quite important. We estimate for certain reasons that it might become the most common so-called recessive form of CMT2. So it's not a super rare gene. It's one of the more common genes and most interesting when we looked at the gene and the pathway and I will talk a little bit more about this in the breakout session, we immediately saw that there is actually a strategy here to treat this with an existing drug that has been developed for a different disorder. We are extremely hopeful that this will work out. We have now identified an industry partner who would be willing to market this strategy and finance trials. And if you want to learn more about it, you can come to the breakout session that Steve and I will give. So it's just an example how it sometimes can go from a genetic discovery almost immediately a treatment opens up. Sometimes it takes 20 years and sometimes it's much faster. So yes, I think that's pretty much all I wanted to tell you here and I'm going to give it back to Gilles I guess.

- Thanks Stefan, thanks everybody. I think we're ready to go do the breakout.

- Thank you all for staying with us in this breakout session. So this is about the demyelinating CMT forms. So this is type 1, X and 4. And because these diseases, as you have heard already before they are caused mostly by mutations in Schwann cells, which are the cells responsible for forming the myelin along the nerves. One of the biggest challenges has been to really target treatments towards Schwann cells. So this is the first slide that I have, which illustrates the progress we have done in terms of achieving delivery of genes to Schwann cells. You can see in this diagram here of the human body, all these orange lines that actually the nerves. So they run throughout our body. We have small and big nerves and Schwann cells are responsible for forming myelin all along these nerves. And usually you need thousands of these cells to really cover the whole length of the axon. And you can imagine that the nerve starts from your lower back and goes all the way to the big toes. So it could be over a meter long. So one of the first issues here is that we need to target Schwann cells to treat demyelinating CMTs because we either need to replace non-functional genes, as I explained before, or because we need to suppress toxic genes. When I say toxic genes I mean, you don't feel a toxic effect because I saw a question, it's just, we're talking about the effect in the cell. So that mutation or that genetic problem causes a toxic effect inside the cell and the cell eventually gets degenerated. So that's what we mean when we say toxic genes. So we have to deliver the genetic therapies to Schwann cells and we also have to use precision medicine here. So one of the biggest efforts was to develop a cell-specific expression. So that means to restrict our genetic therapeutics only in Schwann cells and not have them operate in other cells in the body. And we use a specific guiding DNA molecules to make sure that they only operate in Schwann cells. Another important question was how to access Schwann cells. How do we get our therapies to all these Schwann cells along the nerves? And for this we tested various delivery methods, including an injection of vectors directly into the nerve, which is not easy to apply in the clinic. We also used intravenous delivery, which requires really big amounts of the vector and may not be so feasible. And finally, we found that the lumbar intrathecal injection, which is done by a spinal tap and it's something that clinicians routinely use for diagnostic purposes can really provide a good access to the nerve roots and to the nerves. And so by developing these optimal tools for delivering gene therapy to Schwann cells, this can benefit all demyelinating CMT forms, not just the ones that I will discuss in the following slides. So the first example and the most important disease that we've been working on for many years now is the CMT1X. So just a brief introduction to this CMT type. As you may know, this is the second most common type of all CMTs and the disease is caused by a great number of mutations over 400 different ones, affecting the gene that encodes for connexin32. And connexin32 is really found in Schwann cells and forms very important channels of communication between the myelin sheath and the axon. And so when this gene is not functioning properly, these channels are lost and the whole balance in the cell is disturbed and that leads ultimately to gradual demyelination and at the same time also degeneration of the axon. So there has been a lot of effort to really understand how these mutations cause the disease. And so clinical studies

in many CMT1X families, as well as a lot of research in experimental models of the disease have really demonstrated that it's a loss of function of this gene that causes the nerve damage in patients. And so this allowed us to come to the conclusion that the way to treat this disease will be by replacing the mutated genes. So we are developing a gene replacement strategy for CMT1X. And so I have some just highlights from the work we're doing using currently experimental models. And we are hopefully very close to translating that to the clinic in the near future. So you can see here a nerve which does not have any connexin32. There's a lot of destruction of the myelin sheath and also a lot of degeneration of axons and inflammation. And if we treat this nerve with a vector that produces the healthy connexin32, we can achieve a lot of improvement in the structure of the nerve. And we can also see that we can have a functional benefit. So there is improvement of the speed of conduction along the nerve and the important, which is shown here on the right compared to an untreated nerve. And the important point here is that we can achieve this benefit both when we treat at early stages before there is a lot of damage in the nerve, but also when we treat at later stages after the damage has already developed in the nerve, which is very meaningful in terms of treating patients in the future. That means that we can provide the therapeutic benefit even at later stages of the disease when patients have already more advanced problems with the nerves. Another important issue with treatment for CMT1X was the fact that I mentioned before, the fact that we have many different mutations. So there are many different ways that the mutations cause damage to the protein and its function. So we wanted to make sure that our gene replacement therapy would really be effective for all different types of mutations. So we're treating now models of the disease that expressed representative mutations reported in patients. And you can see here two examples. So the R75W which is one frequently reported mutation and the N175D, this is just the number of the mutation. And what is important here is that we could demonstrate also a benefit in these models with improvement in the muscle strength and improvement in the nerve conduction after replacing the connexin32 gene. And this is ongoing work supported by the CMT Association and the NDA, but it's very important because it demonstrates that gene replacement can be effective for all different types of connexin32 mutations and could potentially be useful for all CMT1X patients. So we're very excited at this stage because we just recently actually signed agreements with a major gene therapy company based in Boston for helping us working with us to bring the CMT1X gene therapy project towards translation into the clinic. So with support from the industry and through this partnership, we are going to optimize the vector for clinical use, perform a proof of principle dose response study to find the optimal amount of the vector for treating the disease, to evaluate possible toxic effects, because that's also important before moving into clinical applications. But I should note that we have not seen any side effects from our work so far. And then the company will hopefully take over the project to go through the regulatory approvals and finally reach the stage of clinical trials. And this is the path really that we have in front of us towards bringing the treatment to you, to the patients. So we're very excited about this development. Now, I'm going to the second example of demyelinating CMT that we have been working on for almost five years now. So this is CMT4C. It's a rare type of CMT, but it's the most frequent among the CMT4s really. And it's also

a neuropathy that is caused by mutations in a gene that is specifically important for Schwann cells. So it's a product that is necessary for Schwann cell development and function. And so in this case, we really need to, again, replace this gene specifically in Schwann cells in order to provide a therapeutic benefit for the neuropathy in CMT4C patients. So we have tested various approaches to treat CMT4C, and you can see an example here on the left. This is a nerve without having the function of the CMT4C gene product. The myelin is very thin. The nerves do not conduct very fast. And so there is weakness. When we treat with the vector that replaces the SH3TC2 protein, which is the CMT4C gene, we can achieve improvement in the myelin formation, and we also achieve improvement in the nerve function, in the muscle power and in the speed of conduction. And we have now with ongoing support from the CMT Association, developed a new therapeutic vector that can be applied in the clinic because it's the same vector that is used for spinal muscular atrophy, the packaging of the vector. And we were able to package the CMT4C gene in this vector, and we have shown already improvement in the model of the disease. So again, here, we're very excited because we're almost finishing the negotiations for agreements with another gene therapy company that will help us to translate this project into the clinic. So I'm very excited and hope to be able to make even more progress towards treating patients in the near future. Finally, we have also developed an effort for gene therapy to treat the most common type of CMT1, the CMT1A. So this disease is caused by excessive amount of the PMP22 gene, because patients have twice as much of the gene copy. So they have a duplication and there is excessive production of this protein which has been shown to cause dysregulation damage to the myelin sheath and therefore result in neuropathy. So here, the effort has been to reduce the amount of the PMP22 protein. So that's where the gene silencing comes into play, and there are different ways to do that. So Dr. Svaren will talk to you about the antisense oligonucleotides which is one approach to reduce the gene product. And we have been working on another approach with RNA interference to block the gene message and reduce the amount of the protein. And now we have a three-way collaboration supported by CMTA with Dr. Svaren and Dr. Steven Gray from University of Southwestern, Texas. Dr. Svaren is an expert in the biology of Schwann cells and gene regulation, and he's helping to develop ways to silence the gene and to target it specifically to Schwann cells. And Dr. Gray is an expert in gene therapy and he's optimizing the viral vectors that will be in the best position to get our genetic therapy to Schwann cells. So I hope we will have also good progress to show in the near future for CMT1A. And with this thank you for being with us and I will pass over to Dr. Svaren.

- Thank you. Do you want to advance the slides for me, or do you want to hand over presentation?

- I'm happy to do that if you like.

- Okay. We can do that this way. So I just want to mention, we are all within the CMTA incredibly grateful for Dr. Kleopa's efforts, and it's really led to some very exciting results which we hope will come to the clinic soon. So when we talk about genetic therapies or gene therapies, it includes the AAV approaches or the virus approaches that were just

described, but it also includes other kinds of genetic therapies. And one of the ones that's yielded some exciting results is antisense oligonucleotides. These are just little pieces of DNA. We call them ASOs and they have the ability to change the levels of gene expression. And particularly for CMT1A where we have elevated levels of a gene known as PMP22, this is a good technology that's somewhat similar to one that Dr. Kleopa described, but this is something that has been also approved for other therapies for things like spinal muscular atrophy. We are anxious to see if this can be applied to CMT. In fact we had developed a collaboration with a company known as Ionis, which is a leader in this area, and they were able to show that the ASOs that they developed were able to lower the levels of PMP22. And it not only arrested the neuropathy when they treated these models, we actually saw some improvement as well. We don't know yet if the improvement will be ... in human trials, but we're very encouraged by these results in these animal models. And in fact, the fact that we could see this improvement also provided a proof of principle that approaches like this, or the one that Dr. Kleopa had just described will likely be successful. One of the things that was mentioned too, is that one of the issues in creating these therapies is to make sure that we can deliver them efficiently to Schwann cells. And one of the factors that's limiting future development of ASOs is that we need to improve the way that we can deliver those ASOs so they don't have to be given a very large doses that might have some side effects. And this is a challenge and a puzzle that we've been working with Ionis to try to solve to allow them to come to a clinical trial for a CMT1A. Next slide. So, in the first part of the session, we really talked about biomarkers and I wanted to go a little bit more in depth here because as we think about how biomarkers can be used in clinical trial, it's very important to realize that the effects that we see in CMT that affect muscle and nerve are originally a product of changes in genes and molecules and cells, and it's a slowly progressive disorder. And so when we imagine reversing that or improving the neuropathy we, first of all, have to change things at the levels of genes and molecules and cells, and this will ultimately result in improved nerve function and improve muscle function. But that can take a little while. So we need some ways to assess whether we're having an effect early on in the clinical trial. And these different arrows that are on this slide are really my imagination of what a successful clinical trial for CMT1A would be. One is that we could reduce the levels of PMP22. This would help to restore Schwann cell myelin. Ultimately that would result in improved nerve function and preservation of those, and these would allow changes to be detected by these nerve conduction studies that we already talked about. And then hopefully that would improve motor function and muscle mass and lead to the positive in calf muscle MRI and the neuropathy scores and other patient reported outcomes. But the first couple of steps are things that would probably happen within the order of a few weeks to a month or so. Whereas the last couple of arrows might take six to 12 months to really show an effect here. So we've been trying to fill in little readouts at the various stages of this process. And we made quite a bit of progress actually in being able to do things like measure the levels of PMP22 in the nerves of skin, and we also have other biomarkers in development. And as I mentioned before, we feel like we're finally in a position to be able to tell a company that we could measure a positive effect, for example, from ASOs within a month or two so that

they don't have to necessarily do a very clinical trial, unless there's something promising that can be showing within a few weeks to a month or so. So this is for CMT1A, but we are have parallel efforts ongoing for CMT1B and CMT1X to fill in these necessary biomarkers. Can you advance to the next slide please? So aside from the gene therapy efforts, I want to make sure to let people know that we're also working to bring compounds or drugs that can be used for treatment of CMT. One of those that's generating a lot of excitement over several years as a molecule called Sephin. It was originally developed in studies of CMT1B, but it seems to have an effect in CMT1A. This was actually developed by one of our board members on the CMTA, Dr. Larry Wrabetz. And you can see here that essentially the thinner myelin that you see in a CMT1B model when treated with Sephin really creates myelin that looks much better. And a company known as InFlectus has obtained a use patent and orphan drug designation both in the United States and Europe. And in fact they've worked with members of our Scientific Advisory Board, Dr. Michael Shy and Maurizio D'Antonio to work in different models of CMT1B. In fact they think it works in both 1B and 1A and they have completed a phase one clinical trial for CMT in Europe. Phase one clinical trial is meant to show or test whether the compound is safe and it passed that test. And they're planning to start a phase two clinical trial for CMT1A in Europe soon. We're also working with them hopefully to bring a clinical trial of this compound to CMT1B. Hopefully that will happen as well but that'll take some more time. In addition to this candidate drug ... can you advance the next slide? ... The CMTA has also invested in other candidate compounds that can be used to treat both CMT1A and 1B. Next slide please.

- I can't advance John, I don't know. Maybe I lost the... I cannot advance the slide.

- All right.

- You want me to share my screen or?

- Yeah, that's probably our best option. So I'm going to stop sharing for Dr. Kleopa and then John, if you want to go ahead? You should be good. This give everyone time to stretch. Oh, reach for the stars. Yes, Jonah. Thank you.

- Okay, I think we were about here before. So in addition to the drug that I just mentioned here, we have just recently improved several projects that are testing different drugs. One of this is a drug that has originally been developed for misfolded proteins, which is actually quite common in the case of CMT and has also been developed and tested successfully in animal models of Alzheimer's disease. This was a project that was developed by one of my colleagues at the University of Wisconsin, Luigi Puglielli. And he's going to be applying these drugs to CMT, both CMT1A and CMT1B. In my laboratory, we've screened a lot of different drugs and there's one FDA approved drug that appears to have good potential to lower PMP22 levels and with support from the CMTA that was recently approved, we'll be doing further testing on this in the animal models for CMT1A. And we have several additional candidate drugs that have been proposed. The proposals are being prepared and they'll be under review for CMTA funding. So we're working forward really to look at

both gene therapies, as well as a candidate drugs for treatment for CMT1A and CMT1B. So in the last few slides here, what I have is actually a subtype by subtype summary of all the activities that we have for different types of CMT1 as well as X and the CMT4. And I'm not going through a lot of these details because we've actually covered them already. But I just want to have in one place, all the efforts that we have going for each of these subtypes so you can see the scope of the things that we're trying as well. So, for example we just covered a decrease in the level of PMP22 using ASOs and we're working with them to improve their delivery. Dr. Kleopa mentioned the gene therapy approach using the virus. Again, this is trying to accomplish the same goal. We are working with a company known as Toolgen which is developed this CRISPR CAS9 strategy which otherwise known as genome editing. And we're there working with our testing capabilities of the CMTA to test this type of gene therapy in models of CMT1A. And I just talked about this new project that was approved in our lab to try to decrease levels of PMP22. In addition to reducing that PMP22, there are several different targets, some of which we've already talked about. One is Sephin which I covered. We are looking at the axon degeneration pathways. So Dr. Scherer mentioned that eventually the progression of CMT is due to attrition of axons. And there's some exciting new things to try. And this is another area that we're moving forward to. There's been a lot of interest in another class of drugs known as HDAC6 inhibitors, which have been tried in various types of CMT. They've done some testing in CMT1A in partnership with our testing facilities in the CMTA. I think so far for CMT1A, the results have been a little bit mixed. And so there's going to be a barter based testing of this class of drugs and other types of CMT. And I also mentioned this misfolded protein pathway, where there are candidate drugs being developed and which can be tested, and this project is moving forward as well. So in addition to all these efforts, some of which are partnerships with all these companies, we have major efforts to move forward on biomarkers and getting ready for clinical trials. And this is really fundamental to be able to move any of these things into clinical trial. And this is in partnership with the Inherited Neuropathy Consortium and all the great CMT neurologists that we have in our broader network. So that's the summary for CMT1A. CMT1B, again, we already covered InFlectus and their testing of Sephin. The mouse studies have been very positive and this drug has already been through the phase one safety trial, and we're hoping that this will come to a phase two trial in the next year. Another expert in CMT1B who's in our Scientific Advisory, Board Maurizio D'Antonio, at University of Milan. He has other compounds that hit similar targets as Sephin. He has different ways to approach those and some of those are looking quite promising. And I already covered that my colleagues project on the misfolded protein pathway, and then CMT1B we've had an active project to look at this axon degeneration pathway. So again, we have several parallel efforts to bring therapies to that. And then in the past summer there's been approval of a really a major biomarker project for CMT1B which will help us to bring to light additional biomarkers and really to get ready for clinical trials, which will employ all the types of biomarkers that I outlined earlier. And CMT1B's a little bit behind 1A, but with this new project, we're hoping to bring 1B up to the level where we have good biomarkers as well. This is CMT1X. So with the support of the CMTA we've been creating additional mouse models for that to make available to Dr. Kleopa as well

as other partners that we have. These have been created by Dr. Charles Abrams in Chicago, also Jackson Laboratories. And then testing has been set up as available through Psychogenics or also through Jackson Labs. And Dr. Kleopa really summarizes very exciting findings. So I won't add too much more to those. We're also moving forward to test this axon degeneration pathway that Dr. Scherer move forward with. And in parallel with all these efforts, we have biomarker projects to again, prepare for clinical trials for that. There's some other projects that are under consideration that we'll probably add to this list in the coming months. But we have a major conference or a symposium of CMT1 experts soon to come where we can evaluate other things as well. And then finally, this is a summary of CMT4. So Dr. Kleopa outlined his very exciting experiments where there's really some success in the animal models. And he mentioned this upcoming partnership. So we've remained busy throughout all the coronavirus shutdowns. And so just last month the CMTA board has approved a new gene therapy project for CMT4A. This is another type of a recessive CMT. And this was with Dr. Steven Gray at UT Southwestern, who has already been mentioned. He's really one of the leading experts of gene therapy in our country and is also connected to a lot of different companies. In fact, he's already been leading ongoing clinical trial in collaboration with NIH for a type of CMT, which is known as GAN. So he's really quite accomplished and we're very excited to have him. He's also a member of our Scientific Advisory Board. And since we approved this project, we already have a company partnership that's in discussion. CMT4J, I just wanted to mention that there was actually a project that was developed. It was originally developed independent of the CMTA, but this was with a company known as Neurogene. That's another gene therapy company. And again, Dr. Steven Gray was involved in this project as well. We are collaborating with them now to support a natural history study, which is required for this gene therapy to move into clinical trials. So we've been trying to collaborate with them to be a good partner to facilitate movement of this to a clinical trial, which I hope will happen sometime soon. And then finally, last but not least, we have a CMT4B1 or B2. We just funded another project led by Dr. Bolino and Dr. Pareyson at University of Milan. Dr. Bolino has developed a candidate drug that she's moving through some mouse drug trials. And Dr. Pareyson is a CMT neurologist who will be in parallel doing a natural history study and some other clinical trial readiness activities. So I realize this has been a whirlwind tour through all of these types of CMT and we really have a lot to talk about and I think we're approaching the end of the session. And I think we can come to questions, I think in that when we come back to the main panel. Laurel, am I on time or not?

- You're timing Dr. Svaren is absolutely perfect. So we are expecting our friends from axonal to pop back into this main Zoom hub any minute, and here they come now. So everyone sit tight, please.

- Wow, that is impressive. I mean, right on the nose. Right on the nose. It's like rehearsed.

- See how it works, Sweeney, just like that.

- Preparation is the key to success, right? Okay, so Gilles, if you could talk so that you come to the front of the panel.

- Hi, I'm back.

- There you are, sir. Okay, I want to make you a co-host again, although it's not letting me. Is Sarah back?

- I knew I had to go to type two to keep it on Stefan, because we only gave him three slides. He's taking two hours to go through it.

- Our timing was so perfect.

- [Gilles] You guys are awesome.

- Right when he rapped, you came into the waiting room.

- Stefan was starting his conclusion, which might take him a couple of minutes, but I think the one thing I want to re-emphasize is STAR is just about a hundred percent supported by the CMT community. And by the way, this is a very conscious decision we made early on not to seek government money, big grants from charities. We don't do any big fundraisers. We don't spend much money on marketing, and because those cost a lot of money and cost a lot of time. And because this is supported by you and so well supported, we basically have very, very... Oops, there we go. Excuse me. We're really, what do we call, best-in-class financials. Our overhead last year, I think was just below 13% which by any standard is world class. They usually find world class is 15 to 20. It's been improving and we're very proud of it. But again, one of the main reasons is we spend most of our money on what you just saw today, between the patient/family conference and all the community activities and STAR, which is of course the biggest by far chunk how we spend our money. But this is thanks to the community. This is your program. It's for you and by you and I want to keep emphasizing that. And in times like this year has been very helpful for us as a community as we come forward. And we're actually having a really good year, even though we were very worried coming in. By the way, this is recognized and you don't have to take my word for it. All the major rating agencies give us the top score. I also encourage you anytime you look at a charity, you look at the RS findings, for example, because it's very telling about how they manage your money. But we have this four stars Charity Navigator rating which is very hard to get. They're awarded to less than 1% of the charities and they raised the bar three years ago. So we're very proud of it. I can tell you, the team has worked really hard on that and it's not easy to get. The other point I want to make, which we're very proud of, is very unique to the CMTA, I think is about 20% of every dollar that we get in comes from the board. And of course it means we have a wonderful board, but it also means that the people who make decisions, now, the board is the place where all those decisions that made. The funding decision, the strategy. Those people really are putting their money where their mouth is. They're really voting with their dollars. They are major funders of this program. We are all completely all in on this. And again, we're making decisions on your behalf because we're one of you. We all have ... We're all involved. We're all part of the community and we're voting with our dollars. And the last point I want to make, it's also very interesting because our whole strategy is based on partnership. When you spend a

dollar on the CMTA, down the road, there will be a company that's going to spend 10 or a hundred dollars to multiply this. And you've seen this in some examples, some of the docs have talked about, where initially we might've written a five or six digit dollar check, but now there's companies coming in and writing seven to eight digit dollar checks, and it's starting to happen. It's very exciting to see happening because now we see already investments. They're just like seed money in the VC world now is leading to much bigger investment from our progress. We're leveraging the dollars that we're spending. So I just want to make sure you understand this. It's all about us, it's all about you as a community and in a way, at leads to my last slide, which is really that we all have a role to play. This is our program. And you saw a lot of ways today, how to get involved and how to help. I just put a few bullet points here, you know, between taking part in the patient registry, going to Centers of Excellence, you know, joining our program where we link patients with partners, and then great community outreach through social media, emails, etc. From a support point of view, we just secured a \$150K match for the rest of the year. So I think we're going to have a very good year considering the pandemic and I think we want to finish very strong because I think we're funding more programs now than ever in the CMTA. I know Jeana mentioned about, we got this really great program that was just started. And as a conclusion, when I started in the nonprofit world, and then finally Mike told me, always there's the three W's, work, wealth and wisdom. That's how you can help. And you got to pick at least two of those. One's not enough, okay. So keep that in mind. And then we're going to close the session and go into the Q and A with the docs, and I'll turn it over to Laurel to let us know which tough questions we're getting.

- Thank you Gilles. So what we are going to do is I'm going to reach out to Jeana and Amy, we'll go back and forth and take some questions that came up during demyelinating or axonal sessions. So Jeana, why don't we start with you, if you could feed the first question and we can figure out which doc should answer that.

- Okay, well I'm not quite sure who this one could go to, but if not knowing the subtype or necessarily the type, how important is it right now to do the genetic testing to find out your subtype and or your type of CMT to participate in the trials?

- Stephan.

- So, yeah, Gilles, thanks a lot. And I also want to mention one other thing before I answer. I feel like talkative today, Gilles. The scientists here, we do this completely in a volunteer basis. We don't get paid for this. So we're really into this as well. So it depends a little bit on the trial.

- I'm sure there are trials that are more broad where you don't need to know your type necessarily, your genetic type. It really depends on the trial. But I would argue for most trials that really try to figure out a new therapy, you're typically being asked to know your type. But Kleopas could add to that as well.

- Yeah, sure. I think that it's a requirement before we discuss gene therapy participation. It's impossible without knowing the type. So although everything is at the experimental level right now, and it may take a few more years to reach clinical trials, without knowing the exact type and the exact mutation even in some cases, it will not be possible because the gene therapies are so targeted. They're tailored to the cause of the disease as we explained.

- That's a great answer. Thank you. Amy, do you have a question please?

- Yes, I do. So one of the questions that came in was on gene therapy and what the goal is. Is it to stop the progression of the disease or is it to reverse symptoms? Kleopas?

- I guess, yeah, my view on this is that, yeah, for sure the first goal will be to stop the progression, so to preserve the nerve function that the patient has. And in some cases or in many cases I hope that we will also be able to reverse some, most likely not all disability. And it will also depend on the age and the stage of the disease that the patient is in. That would be very determining of the response. But of course this remains to be seen because we haven't reached the patients yet, and it's a different situation, but from what we see in the experimental models, that's what I would be a realistic goal.

- Okay, excellent, thank you. Jeana.

- Steve, I believe this one is more for you. Is there a way to take any type of supplements or the supplement NAD to slow down SARM or CMT?

- So that's a good question. Somebody was paying attention. I'm giving you an A on this quiz. If SARM1s role is to degrade NAD, can you take dietary NAD and help your axons out? So theoretically that's possible. I can't remember the name of the supplements that seem to have that ability to sort of increase your body's NAD. It's never been studied to have any effect in neuropathy. So I wouldn't say there's any evidence for it, but the theory, if you could keep NAD levels up and axons that it might help them, I think is sound. I don't think it's even been done in an experimental mouse model yet though. So I'm open to the possibility that is true, but I'm a skeptic until somebody has done an experiment that sort of shows itself.

- Thank you. Amy, do you want to squeeze the question in before--

- Yes, we had a couple of questions on gene therapy for CMT2A and maybe I can just lump some of these together, because it seemed to be a common theme here. With 2A gene therapy, what is the approach? Would it be a knockdown and replacement approach or delivery of a healthy gene? And then a similar question, a related question would be, what is the proposed delivery method? Would it be AAV or some other delivery? And then there was another question about dominant versus recessive forms of CMT2A and how that may differ from a therapy standpoint.

- So those are all good questions to make sure we're clear on. So the current vision is to use AAV nine, which is the virus that was used for

SMA to inject it into the spinal fluid. So, you know, with a spinal tap, inject the virus into the spinal fluid and the virus will contain two different things. It will contain a normal Mitofusin 2 gene, and it will contain probably a small interfering RNA that would essentially decrease the level of the two mitofusin genes in that person that they were born from one from the mom, one from the dad. So you're going to try to decrease the expression of the normal cells Mitofusin 2 and replace it with another Mitofusin 2 gene that you put into the same vector. So that's the theory. It works in practice. Will it work in the animal model and in the human is sort of the steps that we're looking at. Did I miss anything in there again?

- There's a question that I saw in the chat, this confusion about the CMT2A. So CMT2A is this very specific type of CMT. It's a CMT type 2 sometimes called axonal CMT and the gene is Mitofusin 2, MFN2. Many years ago, people thought that another gene may also cause CMT2A. This gene is called QIF1B. But the community has basically decided that that QIF1B, Q-I-F-1-B is very likely not a cause of CMT, okay. And CMT2A means it's always dominant, okay. It's not recessive. What does dominant mean? Dominant means typically one of your parents or one of your children also has CMT. The other form is recessive. Recessive typically means your parents never had CMT, and quite likely your children will also not have CMT. This is a longer thing to say it, this never happened, but as a rule of thumb that's what it is.

- Thank you. Well we're a few minutes after the hour and I just want everyone to know that we are going to look through chat. We do get a printout from Zoom so that we can address the questions that we haven't gotten to today. You can also email me. Everyone should have my email address because I sent out the digital agenda guide. You can email your questions to me and we will get them filtered to the right people if they have not been answered yet, but out of respect for our amazing presenters' time, I think we are going to wrap now. My email address is in the chat. If anyone needs us at the CMTA, we are here for you. And I want to thank our amazing panel of speakers for sharing their time and talents, their Saturday with us. We could not be more appreciative of your time and your dedication to finding a cure or treatment for CMT. And I want to thank our amazing staff at the CMTA. This was truly a teamwork to put this conference together. And most importantly, I want to thank all of you, our community members. It was a privilege and an honor to have you here today, and we wouldn't be here without you, and we wouldn't be pushing all of these programs, initiatives, events, and fundraising forward without you. So thank you everyone for being with us today. I cannot go without two things. We're going to play a really cool video for you if you missed it this morning. As the video wraps, that will be the end of the conference, but I want to thank Sarah Gentry for being our IT wizard today. So on that note, thank you all. We hope to see you again soon at a virtual program. And here is the closing video.