- 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 breakouts. This slide is just a summary of what we've covered. So I'm going to use it just as transition slide.

- So, my name is Steven Scherer. I'm a neurologist at Penn and I've been doing CMT for all of my adult career, I think, and Stefan Züchner will join us at the second part of the talk so I'm aiming to do mine in 20 minutes leaving 15 minutes for that. I'm challenged, I'm challenged. So my goal here is to take us through sort of the state-of-the-art of what we're trying to do to treat the forms of CMT, where it's the neuron that's the problem. So these would be axonal forms of CMT and the most common of these are what is called CMT 2A and these are caused by dominant mutations of a gene called Mitofusin 2 and to give a Stefan Züchner a shout out, And what we know is that people with CMT 2A have both a mutated Mitofusin 2 gene and a normal Mitofusin 2 gene and it's really difficult and challenging to think about how we're going to treat a disease where that's the case but the strategy that's been imagined in the strategy that is being generated by our partners in a company called Passage, which is based out of the University of Pennsylvania where I work, is to basically knock down both copies of the Mitofusin 2 gene and replace them with a viral vector, with a normal Mitofusin 2 gene. So this strategy, if it were to work would basically mean that the Mitofusin 2 gene has to get into the neurons that need it. So the ones that make our peripheral nerves and continue to suppress both the mutant and the wild type Mitofusin gene that the neurons were born with. So this is a great idea. The work is going forward as we speak. They're going to use the same viral vector called AAV nine that was used for the successful trial of spinal muscular atrophy. That was mentioned by Kleopas Kleopa a moment ago and this has been, this project has been greatly enabled by an investment that CMTA association made in two rat and developing two rat models of CMT 2A and so that's what I'm going to show you in the next slide. So, the idea is this: we basically made the rat to have a known human Mitofusin 2 mutation. We created the identical mutation in a rat. What I'm showing you in the middle panel is the size of the nerve conduction amplitude from a rat that's normal, a litter mate and it gets bigger and bigger and bigger as the rat goes from eight weeks of age, to say a year of age to see the top line, gets bigger and bigger and bigger. The litter mates of these rats, they're about 10 rats in each group. It goes up for a time just like their normal litter mates and then it sort of levels off and even goes down. So this shape of a curve is completely different than what it should be and it's the same rats that are being studied every few weeks. So we sort of can visualize how the neuropathy is developing in these Mitofusin 2 mutant rats as they age. It's just what happens to people I might tell you. And then if we look at the nerves that we're recording from a set point in time, this happens to be taken to 28 weeks of age. The nerve on the top panel looks normal and the nerve lower taken from one of the litter mates that has some mutation, you can see has many fewer of these model native excellence then it should be the case. And that's why the size of this response is about half, it's about lost about half the myelinated axons and the response is about half as big. So it doesn't take too much imagination to think that if we could inject a virus here into the rats prior to the onset of disease, the virus got into the cells that needs to get into and let the animals live. That if the animals, whoops, we've got to go back. If,

instead of being this shape of a curve that the nerve response has stayed big, like I'm showing you on the top tracing, that would be a strong indication that the viral therapies work and furthermore, when we sacrifice the animals I looked at the nerves at the end of the experiment instead of looking like this and the lower panel, they would look like this. So that's the concept. I think it's fundamentally sound. What we need to do is inject the virus before the disease starts and just let the animals live for a year and follow their nerve conductions as they age, and at some point decide that we're going to look at the nerve cytologically and see if we've done what we think we needed to do. Now, it's been there a couple of different ways to inject the virus. I think the way that it's being favored by most people around the world for CMT work is to inject the virus into the spinal fluid, which would be in this space right here, where it would gain access to the motor axons in the spinal cord, enter the sensory neurons here in the dorsal root ganglion. So the virus would be injected here. You would infect these neurons that make the motor axons would inject, it would affect these neurons and make the sensory axons and in time the normal Mitofusin gene would come to be found in all of the axons of both motor and sensory neurons and prevent their degeneration. So it's a pretty simple concept. Developing the virus that does exactly what you want is where most of the work is being done at this point and so that's all I can tell you about today but the concept that it might work is very good. It's basically what was done to treat spinal muscular atrophy successfully. So I don't see any reason why if it works in spinal muscular atrophy it wouldn't work in CMT type 2. So there is a parallel strategy that's being developed by our colleagues at Ohio state and they're the group that actually invented the gene therapy for spinal muscular atrophy and they're very keen to do the same thing for CMT 2E. Now CMT 2E is a mutation in a gene called neurofilament light or NEFL. And again, just like there was for CMT 2A there's, there are animal models of CMT 2E and they happen to be mouse models. And the CMTA has already invested in showing that the CMT 2E mouse model develops a neuropathy just like I think it happens in people, and so led by Tony Brown and his colleagues, their strategy is basically very similar to what I just described. They want to knockdown the normal gene, replace it with, knockdown the mutant gene replace it with the normal gene and see if that will actually work to prevent the development of neuropathy. Now, in this case, the same idea, these are now recordings of the nurse from the CMT 2E mouse model that were done with the support of the CMT Association. You can see these dark circles up above that's how the amplitude of the conduction response increases in normal animals and in the mutant animals, their litter mates that goes up for a time and then it goes down. And so what you're seeing here is, again the evidence that axons got sick and got fewer in number and if you look at the nerves after a year, here's the normal litter mates that nerve looks pretty normal. Here's the mutant litter mate. You can see you've lost most of the big axons in the mutant animal. So if we introduced the virus here before the animals get sick and we inject that again into the spinal fluid, the hope is that the virus would infect the motor neurons and the sensory neurons, the neurofilament gene that was in these neurons genetically would be knocked down and replaced by the mutation that or by the wild type gene that you've put into the virus and so normal neurofilament protein with us be made by the neurons that got infected. And if we followed injected animals over time and we saw their responses

look like these dark circles, we would be pretty sure that we've done what we want. We've prevented the neuropathy from developing in the animals, and that would be a therapy that would be quite like SMA. So this is exactly the goal of the exercise is to sort of inactivate the mutant allele and by default, you also have to inactivate the normal allele. You replace it with the wild type neurofilament gene and that should actually fix what is a complicated picture of a dominant disease. So, I have great hopes for this. I think that the group at Ohio State is excellent and so they have all of the expertise that's been earned the hard way through their experience with SMA treatments, which worked in an animal model just like I've been trying to show you here. One second. So let's say that what I've said comes to pass and we were able to show an animal models that we can treat CMT 2A and CMT 2E in a very convincing and, you know, in a very convincing way. This would be, I think, adequate evidence so long as the virus infection is safe to think about how we would do a clinical trial in people with those same diseases. And I'm going to harken back with some comments we heard in the prior session which is what we need to do is to supplement the way we measure neuropathy clinically with biomarkers. And so at least for the neurofilament light thing, we could hope to find neurofilament light which is approaching what is found in an axon. We could hope to do skin biopsies that people who are treated with the vector and find the neurofilament which used to not be there is not present. So that would be a way to show that you've done what you've intended to do doing something as simple as a skin biopsy which is a very minimally invasive procedure. A skin biopsy could also tell you whether you've restored nerve fibers in the skin itself. That's what you can see in a skin biopsy are these tiny little nerve fibers. What we haven't talked about yet but what is also true is we could hope to measure something called neurofilament light in the blood, as it turns out in most neuropathies there's release of the neurofilament from the sick axons into the bloodstream and it's abnormally elevated in the blood, and with the treatment of at least one genetic neuropathy successfully the neurofilament levels in the blood fall towards normal. So those are very good biomarkers. So skin biopsies and neurofilament light in the blood and that would supplement what we do with muscle MRI that John Svaren showed you in the prior session. That would supplement what we do with our nerve conductions in the EMG lab and would supplement what we call patient reported outcomes, which is what people with CMT tell us is going right or wrong with their function in life and the way we measure neuropathy with our clinical exams, which I think most of you who have neuropathy have probably experienced. So that's what companies want to know when they engage over this. They want to know that we have a pathway to doing a critical trial and I think the steps that I'm showing you in this cartoon fulfill what would be sort of the required components of a clinical trial pathway. Now we haven't talked about it yet in this seminar today but in fact in parallel with all the research that's going on, there are clinicians, myself included, but others Mike Shy, Mary Riley, Davide Pareyson and David Herrmann in particular who have been collecting large numbers of patients doing these measurements in the bottom here in the hopes of figuring out what we'll measure in patients when they come to a clinical trial and showing that these were these measurements and CMT 2E and CMT 2A will also be responsive. So that's going on in parallel in the background, given that we can't wait to do that, those kinds of studies until we have something

to test. We need to have something ready to go for a clinical trial just as soon as there's something worth testing. So now I want to go back to something we said before and say it in a different way. So there is at UCSF, a very famous group that's founder, whose founder is Jennifer Doudna, who just won the Nobel Prize this year for the invention of CRISPR CAS9 technology and so she has a whole institute that's devoted to using this technology for treating diseases. There is a group within that institute led by Luke Judge and Bruce Conklin who selected CMT independent of us, talking to them about it as a candidate disease for using this technology as a treatment. And so here's how it work. There's basically a patient with CMT 2E who's donated some skin cells. We grow those skin cells in a dish and we fix the gene and the way that Kleopas showed you, we replace the mutation in the one bad copy of the gene with the normal sequence and we fix the gene and that goes on to being these corrected IPS cells, these STEM cells. We can differentiate those cells into neurons and if these neurons look normal and their untreated counterparts look sick, the way we actually know them to look sick, and I don't have a slide to show you but we already know this is true. And we would have shown in principle that we can fix the mutation for neurofilament light or for that matter Mitofusin 2 or for that matter, heat shock protein beta one which causes CMT 2F. We can fix these two dominant mutations genetically, prove that they have the desired effect in the culture neurons and if that's successful, we can go on and fix the mouse models of the very same diseases. We can basically fix the gene in the mouse by injecting into the spinal fluid the components that make the CRISPR CAS9 technology work. So this is amazingly ambitious, all right. So I'm not going to pretend that the technology has been figured out to nearly the same degree to do this in a mouse or a human as it has been for the gene replacement strategy that I was describing just a moment ago., But if it were to work it represents a completely novel way, a completely independent way of trying to fix the mutations in patients who have various dominant mutations. And so the CMTA has invested in a big grant to this group in the hopes that this technology can be made to work in, on behalf of, for patients who have CMT. And the technology would work for all dominant forms the ones that are being pursued initially are 2E, 2A and 2F, but there's no reason that other forms of CMT that are dominant wouldn't be treatable in the same way. So in the last couple of slides I just want to summarize what I think I've already said. So for CMT 2A, that's the Mitofusin 2 mutations, we have two technologies that we're putting to work. We were thinking about AAV gene therapy which is basically reducing the endogenous gene that's mutant as well as its wild-type counterpart and replacing it with a gene that's in the viral vector. The CRISPR CAS9 intends to fix, genetically, the broken gene directly. I haven't talked about it here but there is at least one company that's come up with a strategy for fixing Mitofusin mutations with small molecules, that's called mitochondria in motion and I don't have more to say about that but there are other companies out there with the different approaches to the problem. We've mentioned that preventing axonal degeneration would be an ideal way of treating neuropathy and it might be for CMT 2A as well. So that would be inhibition of SARM1 and there are some other companies in our that are in discussions with us that have other ideas of how to treat CMT 2A and finally the Inherited Neuropathy Consortium, which is a clinical group, is trying to get us ready for clinical trials. Much of the same thing can be said for CMT 2E where we

again have authentic animal models. We have human STEM cells from patients which have been used to make drug screens by Liem Columbia and by Mario Saporta of the University of Miami and they have found compounds that basically do have effects on these STEM cells. There's the two same approaches that we've already discussed which is CRISPR CAS9 and the gene replacement strategy. We're not quite as far along with the clinical readiness because CMT 2E is rarer. There aren't as many patients with CMT 2E. So we don't have the numbers of patients to do the clinical trial readiness with but we are working on it and at least analyzing some patients in this way, just so that if there are successes in the lab that we're ready to apply them to people. So, Steven, I think I finished in 20 minutes, 19 actually and I think I'm going to drive the slides for you or you can pick up from here and become the presenter, whichever you prefer. What do you want to do?

- I think it's just, just keep driving Steve.

- Yeah, you just have to say next slide whenever you want it.

- Exactly, I have a few slides and per se, I, as you were talking, I was busy typing. That's a good question Steve. You know I, I'm happy to review some of your genetic reports. There were lots of questions about that and Amy, Amy can give you my contact but, but please, please be patient because it seems like a lot of people have questions, and then it's ... there may be a limit what's possible, but we are here to help for sure. And every family, every patient is, is very important to us. So really I want to give you again, a bit of an overview and share some thoughts on the genetics of the CMT type 2s. As I said earlier, the CMT type 1 the genetics is worked out pretty well by now. There's still question marks but, the focus in terms of, of this diagnostic gap is really on the axon or the CMT type 2s, and I can see it in the questions. The questions are broadly about sort of what does my test mean on sort of that needs more education, maybe Amy thinking the other type of question I see is I got a test but it says it's, it's a variant of unknown significance or my doctor isn't sure or I have two results, which one is the real one. And, and that is sort of the area that I mentioned previously of what is sometimes called the VUS variants of uncertain significance. It's like, it's a bit like when you think about gardening and yeah if your, your garden with tomato plants and then you have all these weeds in between. Now the weeds they, they are pretty much harmless but, but you know, they they're and if you don't know what tomatoes look like, you may get confused. So and it's very hard to sort of decide sometimes what is the real variant here, and sometimes it's impossible. So it's, it's a major problem. It's we are very aware of this. We have projects devoted to this issue for instance, and I don't have slides for all of this. So I just keep telling you, we have, for instance, an initiative where we collect sort of genetic reports and this happens typically through doctors and physicians and this is very international. So, the idea is to simply collect the variants that have been observed in CMT patients and then have them on a website without names, without birth dates and anything just, just the particular variant. And everybody can, can access this website, patients doctors and so on, and especially also international. So, and doctors can even leave sort of certain comments and opinions on specific variants. The idea is that over time, by

collecting these a picture of will emerge that some variants are clearly being reported again and again in CMT patients. So it's becoming pretty clear those are, those are harmful variants and others may be then reported over time also in individuals that don't have CMT. So then over time, maybe it may emerge and those that those variants are more benign. So, so that's, for instance one initiative, we do this whole VUS topic also harks back a little bit to the biomarkers maybe. There are broad, broad, broad biomarkers like the MRI, the imaging studies that you saw before and then sometimes to have biomarkers just very very specific and I will show you one such biomarker in two slides down. With these very specific biomarkers, it may be possible to not just do a genetic test but then if there's a VUS to look at this particular biomarker and say well, the biomarker's negative. So that particular VUS is probably benign, right. So having other types of tests, could complement genetic diagnosis. But the whole VUS topic is a big problem and frankly, the more gene tests we do and we do more every day, not just in CMT but in all of medicine. The, what genetic tests have been done the more of VUS are being sort of emerge. That's a big problem. The other, the other thing I want to sort of point out what we are doing actively and we that is more narrowly here in United States, the INC the Inherited Neuropathy Consortium where Steve is a member, I'm a member and really other great physicians and scientists are members. And there's a pretty broad research program that the INC sort of is an umbrella for. A lot of it depends really for you the patients with CMT to, to participate. It's a research program, meaning if you come to Dr. Scherer's clinic, I'm sure he will always ask you to join a research study and you have to sign some additional paperwork, but that is the starting point of to participate in a research study which can be quite passive, meaning you basically agree that your data is being shared in a secure fashion with the other scientists, but it could also be a more active role where you participate in certain activities, maybe more intense measurements or genetic studies and so on. So, I just want to say that it's very important. This is sort of a partnership between you, the families and patients and the scientists. And it is a research program meaning it's not a, it's not a clinical program, right. It's, it doesn't have a real timeline. Although I hope you get the sense that many of us are very driven to get to solutions in a timely fashion and push the field forward fast, but it's not in timeline. Sometimes things can take a long time and sometimes the reason is simply funding. We have hundreds of DNA samples. So we simply don't have the funding sometimes to perform advanced research genetics. So it, it takes about to get funding. There are some times entryways like personal research genome studies. We do and, and Amy, can you tell you more about this too, where we can sometimes speed things up for, for particular individuals, but typically it's, you know, it's a process. And so let we see here on the left side, you saw a similar pie charts before. The message really is here not so much the particular numbers, but the message is that there are still many patients out there with other genetic diagnosis and as I said, you need to know your gene. You need to know sort of your home address for two main reasons. One is these specific therapies, like the genetic therapies. You just need to know the gene otherwise you, you don't know what to treat, right. And then of course, there's the hope that we can actually develop some broader therapies. Steve mentioned this SARM, SARM1 gene there's lots of excitement about it, and we'll see what happens there. It's so far the

deep broad therapies have been somewhat of a disappointment but to be fair, 10 years ago there was almost no sort of visible effort from the pharma industry and this has really changed. So I would, I would expect that you will see some broader therapies also come to light that that may work on different types of CMT. And even sometimes on CMT that where you don't know the genetic diagnosis. Okay, it's definitely that, that hope there too. So, as I said, it's a partnership, patients and scientists, and that is especially true when you do genetic studies and that's the lower part of the slide. The last, the second bullet point there, it has become clear in CMT research, genetic research but also for other disorders the, the next decade we will spend a lot with really coming together as a [?] and, and finding ways to support what we call it aggregate genetic data. Basically, instead of having 10 scientists, maybe in multiple countries, creating their own collection of genomic research data, finding ways to, to convince them to, to bring the data together in one database that these scientists can study, can study this database, they can share this database. There is simply power in the numbers. I talked to Amy the other week. I said, we need 10,000 CMT genomes, 10,000. That's sort of a higher aspirational goal, but imagine today we have maybe the best the greatest biggest database we have in the in the Genesis Project has about 1500 CMT genomes in there. So getting to 10,000 I believe would allow geneticists to do a lot more, to find these more rare causes of CMT, to find unusual variants maybe also to clarify a good number of these variants of unknown significance. So that's sort of what you're striving towards too. And it's not just the science. It needs a lot of organizational growth. In this picture there what the globe map, what this symbolizes is an example, is a gene called ATP1A1. It's a relatively new CMT 2 gene and you sort of see how we discovered it. We had done in Miami under my name you have this Genesis database and we found a signal because we aggregated all these, these, these datasets. We found a signal and the signal was supported by patients that are collected by Dr. Shy for the INC, Dr. Samaan in the Czech Republic Dr. Choi who was in South Korea and then a team down in Australia. So bringing these patients in from the most unlikely places gives you that kind of power to find the signals that's sort of what we mean. Okay, Steve maybe the next slide. And so also just sort of give me some talking points here. What we strive for is high quality science and CMT as you know, it's a rare disease. It has a funny name. When you tell your neighbor, they typically have to ask to repeat what you just said because they don't understood it the first time. They never heard of it, but I just want to assure you that there is really high end science going on in this field. And, and as academics, we always proud of the discoveries we make and when they really important discoveries it's a very competitive then they will be published by journals like "Science" or "Nature," "Nature Genetics." So for us it's sort of a big deal if we can get our discoveries and CMT into these journals. And here's three examples of this, on the left side, Steve already mentioned the discovery of someone, that was actually discovered through an effort that had nothing to do with CMT at first. Dr. Freeman, who is now in Oregon, he studies deep, deep biology of nerve cells and axons in fruit flies and he was simply interested in biology and what prevents these nerve cells and axons and fruit flies to survive longer. So he had sort of his basics, what we called basic science ideas, and he and I met in 2010 it was I think, or nine. And then I was sequencing with the night news technology to CMT

patients and I said, you know what, we can also sequence your flies the same way. I just treat your flies as CMT patients and maybe that will reveal it. And sure enough, that's what we did. We applied the latest sequence technology at the time and then we found these mutations in his flies. In free flies we found like in three CMT patients, he found three mutations in the same gene and the rest is history. And led to this amazing discovery. The, in the middle is a paper that came out last year mostly through efforts from a group around Mary Riley and Henry Holden. They are situated in London and they've both famous for the work they do in CMT and other disorders. And they found this very important gene called RFC1 and the importance really here is, it's a very unusual type of mutation. It's a kind of mutation we have not seen before in CMT. It's what we call a repeat expansion. It's known for a handful of other diseases but it's never been seen in CMT, and they found that this causes a complex type of CMT which is actually not called CMT. It's called CANVAS but it has CMT in it. And and sometimes patients predominantly show symptoms of CMT. So that was a great success and many of us were involved in this industry work and then...

- We are running out of time.

- Oh, and on the left you see the latest, it's the discovery of the SORD gene and I'm going to tell you in the next slide but this is about, Steve next. Okay, so now this is the highlight of the year. This is an example of a new gene where all the good things come together and we are extremely excited. So I already told you. It's a recessive type of CMT. What does it mean? You have to have two, typically two changes in this gene. Typically parents do not have the phenotype but they carry the risk for it and then the child has CMT 2 and because this type of trait is called recessive. So we know it's very common. We know for some good genetic reasons that there are over 3000 patients in the US alone. And the best part is we think it's treatable. And being the optimist here, I think this will be the first true CMT treatment. So on the, when you look at the figures the upper left, this is what they call a pathway and you see there is glucose, which is basically sugar. So this is a pathway where glucose is turned into other molecules. So glucose there's an enzyme C, all those reductase turned into sorbitol, and then sorbitol which is another type of sugar is turned into fructose, which is basically fruit, fruit sugar. So we know, so, and you see the red cross out sorbitol dehydrogenase, this is the long word for SORD. So SORD is sorbitol dehydrogenase...in patients, you patients do not make sorbitol dehydrogenase, meaning they not able to turn sorbitol into fructose. That means the sorbitol doesn't get turned over, you saw the level of sorbitol increases and to prevent this smart people before us have already for other reasons, thought about it. To prevent this you could actually inhibit the aldose reductase. So you don't turn glucose over in the first place, and there are drugs available for this. So sorbitol goes out, that's the idea. When we look at these patients and go follow the arrow there down to biomarker, it checked in a handful of CMT patients with this SORD neuropathy and in fact you can see. The control have very low levels of sorbitol in their blood.

- Sorry to interrupt but we have to rejoin the other group in one minute. So I just wanted to give you the one minute

- Oh, my God, Amy. And these patients to have very high levels. So that is a biomarker, fantastic biomarker you can use for treatment. Number three, maybe the most important. Then we then look in patient on the left or intracellular models, genetic models. The short answer here is we can completely normalize sorbitol levels and these flies, they actually show a neuropathy and it can heal the neuropathy. Then we treat with these types of drugs. So we currently do a natural history study and other things to prepare for trial. In the next slide, Steve, real quick. All right, this is, oops. This is weird, I see a slide there 47. I didn't put it in. Okay, that's fine. So I can just tell you, the pharma industry partner and you need to market it in your truck and we are testing the drug now in our models and this is coming together nicely and I think we will even next year see possibly a first trial.

- I just want to wrap it up. I think you've all basically got a better idea what STAR is an incredibly exciting and successful this thing is. The one thing I want to reemphasize is STAR is just 100% 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 it 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 you know, 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 their RS findings, for example, because it's very telling about how they manage your money but we have this four stars check 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 as 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 are 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 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 check, but now there's companies coming in and writing seven or 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, it leads to my last slide, which is really that we all have a role to play. This is 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'll want to finish very strong because I think we're finding more programs now than ever in the CMTA. I know Jeana mentioned about we've got this really great program that was just started. And as a conclusion, when I started in the nonprofit world and then the finally Mike told me you 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.

- 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, you know, 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. AQd 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 and experiment that sort of shows itself.

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

- Yes, we had a couple of questions on gene therapy for CMT2A and maybe I can just kind of 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 the human, is sort of the steps that we're looking at. Did I miss anything in there again? I'm just

- 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 PIF1B. But the community has basically decided that that kIF1B or K-I-F-1-B is very likely not a cause of CMT, okay. And, and CMT2 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 print out 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 addresses in the chat. If anyone needs us at the CMTA, we're 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.