Episode 56-
Precision Medicine: Mapping the Genetic Code for New Treatments

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Mindy Henderson: Welcome to the Quest Podcast. Proudly presented by the Muscular Dystrophy Association as part of the Quest family of content. I'm your host, Mindy Henderson. Together, we are here to bring thoughtful conversation to the neuromuscular disease community and beyond about issues affecting those with neuromuscular disease and other disabilities and those who love them. We are here for you to educate and inform, to demystify, to inspire, and to entertain. We are here shining a light on all that makes you, you. Whether you are one of us, love someone who is or are on another journey altogether, thanks for joining. Now, let's get started.

September is Muscular Dystrophy Awareness Month, and I couldn't think of any better guests than the three individuals I have with me today to talk about muscular dystrophy and related diseases, as well as some of the exciting advancements that have led to faster, easier, and more accurate genetic diagnoses. Their credentials and accomplishments are far too many to cover, but suffice it to say their work is incredibly impressive and I am so proud to have them here with me today. First up, I have Dr. Stephan Zuchner. Dr. Zuchner is a professor of human genetics and neurology in the role of chief genomics officer at the University of Miami Miller School of Medicine. Next, Dr. Chris Weihl is a professor of neurology, head of the neurology neuromuscular section, and director of the Muscular Dystrophy Association clinic at Washington University School of Medicine in St. Louis. And last but certainly not least, I have my friend

and colleague, Dr. Angela Lek, who is the interim chief research officer at the Muscular Dystrophy Association.

Thank you all so much for being here. I'd like to just start because, like I said, reading your bios made my head spin and the work that you've all done is incredible. So I would love to just have each of you talk a little bit about your areas of focus and really what led you into this work. Maybe we can start with you Dr. Zuchner.

Stephan Zuchner: Sure. Mindy, first of all, thank you for having me here. Happy to participate in this. I actually grew up in Germany and most of my education there. So I went to med school in Germany and ended up doing research work at my university there, which happened to be in the key German center for neuromuscular pathology. In fact, I trained as a neurologist there, but also I trained as a neuropathologist as well. So that was sort of my first deep entry into the field of neuromuscular diseases, basically, as a pathologist. But I did also discover for other reasons, I guess, that I really liked genetics. I was always drawn to genetics, the power of genetics. I vividly remember the first sequencing experiment I did myself as a young doctor identifying a mutation in a patient with neuromuscular disorder, and realizing late night by myself in the laboratory that this single change there put this life of that individual on a completely different trajectory.

We all have our little aha moment, so that was for me there. I was very lucky to get a fellowship to come to the United States to do a research here away from clinic. That was so convincing for me that I, in the end, decided to stay in the United States and make this my full-time profession, being a neuromuscular scientist and economist.

Mindy Henderson: Amazing. Thank you for that. Dr. Weihl, let's switch over to you.

Chris Weihl: Sure. Again, thank you for having me. It's a pleasure to talk to you, Mindy, and to be with the rest of this group. I would say that I did med school and I did my graduate school work at a time where molecular biology and molecular genetics were just emerging, and really understanding how to manipulate genetics in experimental systems was something that was really interesting and exciting to me experimentally. And then seeing patients in clinic and starting to realize that there was likely an underlying genetic etiology to some of the diseases that we're seeing really began to kind of emerge and cement itself. One area, as a neurologist, that we see is probably the greatest breadth of different types of diseases and presentations that can be caused by different disease genes. Meaning that you can see the same patient with a neuropathy or with a muscular dystrophy, yet the number of genetic variations that can cause that disease just felt limitless.

So I think that's really added to this idea of solving a genetic puzzle, solving a clinical puzzle that really made me more interested in neuromuscular disease, but also interested in identifying the underlying pathogenic mechanism.

Another aspect with genetics is once you find the genetic etiology, you really have found the answer. It's not like in some diseases where you still don't actually know what's causing it, you really have gone down to the fundamental roots. And that's just really satisfying and gratifying. And then I would say I started my career about 18 years ago, and I entered into a very large already existing Muscular Dystrophy Association clinic in which there were patients that had been well phenotyped and families that we'd had for many years being seen in that clinic that didn't have a diagnosis at the time because genetic medicine wasn't as readily available for the patients and, in many cases, the disease gene had not been identified.

So it was really at that point that I was able to start, with the advent of newer sequencing technologies, things that you could do on smaller families where the importance of finding a patient from one family or an individual patient that phenotypically was very similar to another patient, and then matching those genetics together. It was a very different way, a very physician-led way of understanding diseases rather than long families and looking at linkage. It was really pattern recognition in the patient phenotypically and then pattern recognition genetically. So I think that's probably what made me begin to be so interested. And then obviously, staying on top of new genetic variations is just as exciting to then understand pathogenic mechanism, and it's really led to just a endless amount of intellectual questions that could be answered in experimental models.

Mindy Henderson: Well, you both have a knack for making what you do sound very easy. I wish that all the time that I could live in the brains of scientists like yours for just an hour or two, and I think it would be fascinating. Dr. Lek, if I'm not mistaken, you've had a 15-year career in research and now, of course, working for MDA. What led you into this field of work?

Angela Lek: To be honest, it was all the publicity around the completion of the Human Genome Project, which was in the early two 2000s, that really fascinated me. That happened while I was in high school. I'm revealing my age a little bit here. But I was super fascinated, super excited by the fact that our traits are encoded within our genome, whether they be good or bad. And then that there were technologies and machines that could be deployed to interpret this genetic code for the first time in human history. That was just really mind blowing to me. And that was what attracted me to the field of molecular biology, which delves into how DNA works, how it encodes genes and proteins. All that was super fascinating. And I pursued some of those studies in college back in Sydney, Australia, which is my home. Along the way, I met my husband along with several members of his family, and they were diagnosed with a form of muscular dystrophy called limb-girdle. It's an autosomal recessive condition with an adult onset that causes progressive muscle weakness and wasting, and loss of independence over time.

So that sort of spurred me on to dedicate my career to neuromuscular disease research, first, during my PhD, which involved trying to understand how a

particular gene called dysferlin gives rise to a form of limb-girdle muscular dystrophy and what the cellular consequences of that were. And then I pursued postdoctoral studies in Boston Children's Hospital, in the laboratory of Luke Hinkle, where I pursued further studies into Duchenne muscular dystrophy and also facioscapulohumeral dystrophy. That one's always a mouthful to say.

Mindy Henderson: Definitely.

Angela Lek: Yeah. Now, I'm at MDA. I started off as a vice president of research, and now I'm the interim chief research officer. I have the privilege of working with leading researchers and clinicians around the world, such as Dr. Weihl and Dr. Zuchner, to help accelerate progress across the entire neuromuscular disease landscape.

Mindy Henderson: Amazing. Well, we love having you at MDA. We're incredibly fortunate. I'm excited to dig into more of the work that you all do every day and some of the concepts that you mentioned. But Dr. Weihl, the term muscular dystrophy gets used pretty broadly in the public. Could you explain what it actually means, and what types of diagnoses fall under that umbrella?

Chris Weihl: Yeah, sure. Muscular dystrophy is an inherited disorder, meaning that you get a variation in a gene, typically a gene that's expressed in muscle, that then is defective and then causes the muscular dystrophy. In some cases, you need two mutations, which is a recessive disorder. In some cases, it's passed on the X chromosome, and so it ends up presenting more commonly in boys. And then in some cases, it can be autosomal dominant, meaning you need just one variation. But at its simplest form, it is a disease of degeneration of muscle and then regeneration of the muscle that then leads to this pattern that we call a dystrophy, which ends up being degeneration of muscle leading to fibrosis and fatty replacement. And it's due typically to fragility of that muscle fiber for variety of different reasons, whether that muscle fiber is fragile because the muscle membrane is somewhat leaky, whether that muscle is fragile because of a mishandling of calcium that causes it to contract in abnormal ways, or whether it's due to mutations that affect maybe the nuclear lamina that then leads to secondarily a fragile muscle. Those are the molecular kind of mechanisms.

But as far as whenever we think of muscular dystrophy, it causes a pattern of muscle weakness often presenting in the proximal musculature, so often the shoulders and the legs. However, there are a variety of different forms and they often have names that kind of describe their pattern of weakness. One form we call limb-girdle muscular dystrophy, and that's a description of how the patient's pattern of weakness would be. So typically shoulder girdles and pelvic girdle. Angela mentioned another facioscapulohumeral dystrophy, which typically cause facial, weakness in the arm muscles, and weakness in the lower extremities. So that's one way that we name muscular dystrophies.

Another way that we name muscular dystrophies are historic kind of eponyms, and so a historic eponym that we think of is Duchenne muscular dystrophy. That

was named after the clinician who astutely identified these patients and kind of characterized them as being a single disease entity. Another one is Becker muscular dystrophy. So all of these are muscular dystrophies. And what I think is important is they cause progressive muscle weakness, and they're due to a genetic etiology that causes either a deficiency or a dysfunction of the muscle that leads for it to be fragile and often degenerate, leading to then replacement with fatty tissue and connective tissue.

Mindy Henderson: Similarly, Dr. Zuchner, I'd like to ask you the same question, but your expertise, if I'm not mistaken, is in Charcot-Marie-Tooth disease and neuropathy. How do those conditions differ from the muscular dystrophies?

Stephan Zuchner: First of all, this name CMT or Charcot-Marie-Tooth neuropathy or disease, it sounds very complicated. What it actually means, Charcot, Marie, and Tooth are three individuals who lived about 150 years ago, three doctors, who were the ones who defined what that is. So what is that? It's essentially a neuropathy, and specifically an inherited neuropathy. So you typically would inherit from your parents. And neuropathy is a disease that affects your nerve, the nerves that run in your legs, in your arms. These nerves connect, for instance, to your muscles. So they make the muscle move. And that is why when the nerves are not working properly, you see somewhat similar symptoms than for muscular dystrophies. You have this weakness, muscle weakness, muscle wasting, but the reason why you have that is quite different. It's not the muscle fiber itself, the muscle itself, it's actually the nerve that connects to the muscle.

Nerves are a bit like the electric cables maybe in your house, in a way. They're sort of wires that transmit information from your brain, in this case. You may have this idea to get up and go and get some coffee, then your brain tells your body to start moving. And to move your muscles, you need that interconnection between your brain and your muscles that... these are the nerves. So neuropathies affect the nerves. That's really what it is. There was certainly the idea early on that... Doctors first studied patients 100 years ago, and they came up with systems to put patients with neuropathies into certain groups. That was just what was possible at the time because of technology, basically. So they became better and better in understanding these groups. There aren't that many groups, and I don't even want to go into the detail here. But there was certainly the hope that once we understand the genes underlying, there may only be a few genes that explain these groups. Doctors are very smart. Even 100 years ago, they understood this is inherited from your parents.

How did they know that? Because they observed that these disorders, they run in families often. So they understood this was something that had to do with the transmission of genes from parents to children. The first gene was found in the early '90s for CMT, and it was a huge success. It did explained a lot of patients, especially for the so-called demyelinating type. But then, pretty quickly, doctors also realized it didn't explain every patient. It did also not explain every demyelinating type of patients. So this was the beginning of a long journey, and we're still on this journey. Since then, scientists have discovered over 130 genes

that can cause CMT or neuropathy. And still, depending a little bit on how you count, between 30 and 60% of patients still don't have a change in any of the known genes.

So this is sort of where we are right now, a tremendous success. Over 100 factors were discovered, the understanding of the categories, the different types of CMT has immensely increased. At the same time, a lot of patients don't know their diagnosis yet. Clearly, many of those, they clearly have some gene underlying. And I guess we'll talk a little bit more about this topic as we go on here. Yeah, I'll leave it there.

Mindy Henderson: Yeah. No, that's a perfect segue actually. I've been told that something called next-generation sequencing is what I'd like to spend a lot of time on today, and talk about the implications of that and what it is exactly. But before we do that, Dr. Lek, I would like to ask you... There are two different ways, in my understanding, that patients get diagnosed today. Some receive a clinical diagnosis and some receive a genetic diagnosis. Can you talk a little bit about the difference between those two things? I personally, until I worked for MDA, didn't realize there was a difference between those two things and what that meant exactly.

Angela Lek: From a high level point of view, and perhaps Chris can maybe expand in more detail afterwards, a clinical diagnosis is a diagnosis based on your clinical symptoms, based on associated with different muscle groups, different parts of your body. And together, they will give rise to a clinical picture that maybe points towards one disease over another. However, it's not very precise. A genetic diagnosis is when you obtain blood from a patient or a muscle, you isolate the DNA, sequence that DNA or do some sort of genotyping panel, and then figure out where the exact disease-causing pathogenic mutation occurred in your genes, which gene is affected. And that way, you can say, "Oh, you have Duchenne muscular dystrophy, you have a mutation in the dystrophin gene. Or you have limb-girdle type 2G or R7 because you have a mutation in your TCAP gene." It's very, very precise. Sometimes a clinical diagnosis is less precise, and it can result in misdiagnosis is my understanding. Is that true, Chris?

Chris Weihl: Sure. I think you did a great job at explaining that, Angela. I would say they're not mutually exclusive, and they work hand in hand. So what I would say is getting a genetic diagnosis is important and becoming more and more imperative as gene-focused therapies are being developed to understand. But I would say that having a variation on your genetic panel, if you don't have the clinical symptoms, I would say that doesn't mean that you have the disease. So you still have to go hand in hand.

Angela Lek: That's true. Yeah.

Chris Weihl: And then I would say that a clinical diagnosis, as we talked about, and Stephan explained it really well, in a patient with neuropathy, which may look very similar to patient after patient, has a neuropathy. We might say they have CMT.

We might even say they have CMT of demyelinating features. That's a clinical diagnosis that then helps us make the genetic diagnosis. Because they may then look at the genetic panel, and so I think often patients get confused. So I know in the field of limb-girdle muscular dystrophy, we say, "Oh, you have limb-girdle muscular dystrophy." As Stephan said, the same is true in limb-girdle muscular dystrophy where about, depending on how you count, 30 to 50% of patients with limb-girdle muscular dystrophy don't have a genetic cause. But that does not mean they don't have limb-girdle muscular dystrophy, just like it doesn't mean they don't have CMT if you can't find the genetic cause. So I think of them, a clinical diagnosis, as kind of an overarching umbrella for many different genetic diagnoses, about half that we know and about half we still are trying to figure out.

Mindy Henderson: Interesting. I hear stories all the time, and what we're going to be focusing on for the rest of this conversation is a lot about diagnostics and treatments. But I hear stories all the time from individuals who have symptoms and they know that something's wrong, and they've been working for 5, 10, 30 years to try to get a diagnosis. And my sort of phrasing of choice has become, "You don't want there to be something wrong, but you want there to be an explanation." So I feel so terribly for people who I speak to regularly who have these sometimes really serious symptoms and things breaking down in their bodies, but they just don't know what it is and they can't get the appropriate help because they haven't been able to pinpoint what the problem is. So with that, I would like-

Chris Weihl: Mindy, I'm sorry to interject.

Mindy Henderson: Please.

Chris Weihl: I caution those patients because they do have a diagnosis, they have a muscular dystrophy. They might not have a genetic subtype. I often see patients get very frustrated because they don't think they have a diagnosis because they don't have a genetic subtype, but they do have a diagnosis. They've got a muscular dystrophy, and it's something we take very seriously and want to help treat even if we don't know the underlying genetic etiology. I apologize for interrupting, Mindy.

Mindy Henderson: No, not at all. That's very helpful. You live and breathe us every day, so I'm glad that you added that. So like I said just a little while ago, one of the most transformative technologies in patient care that I'm hearing about is next-generation sequencing. For anyone listening who may not be familiar, would one of you like to break that down for us in simple terms and just tell us a little bit about what that is?

Stephan Zuchner: Yeah, I'm happy to start this. Basically, it's true in medicine and in science that technology, in general, is a very strong driving force. While we like to believe we'll sit in our libraries and come up with these great ideas, it's often the technologies that help us to break through walls basically and discover new things. So sequencing the DNA is one of these fundamental abilities that really

started what we know as genetics today. And what it means is DNA is the entity that's huge. It's a molecule really, a chemical molecule that we inherit from our parents. Basically, in one way, you often see it portrayed as this long line. It's sort of a long string, and there are four bases, like four letters. We have some 25 letters in the alphabet or so. The DNA language is four letters, A, C, G, and T. Like in a book, with letters of the alphabet, the exact sequence of these letters give meaning to words, to sentences.

So that is really fundamentally what genetics is, being able to read these four-letter code in the DNA and discover, "Oh, they are actually words." We call them genes maybe, and there are sentences. So I would say we're still, in some sense, at the very beginning of understanding the human DNA and its meaning. But first of all, you need to be able to read the book. You need to recognize the letters and the sequence of them, and that is what sequencing technology means. Okay? There have been many iterations of this over the decades, and the latest is called... I guess we ran out of new cool words. So instead of coming up with a new word for sequencing, we called it next-generation sequencing. And really all you need to know is it's just way more effective. It enabled that we can now read a person's entire genome for really less than a thousand dollars now. It's something that was unthinkable of just 30 years ago, simply unthinkable.

Now, it's sort of routine. And it's here in diagnostics, it's available. There are, even now, new iterations of next-generation sequencing as we speak. The latest you might hear sometimes is called long-read genome sequencing. It produces an even better version, a better resolution of the genome. And every time there is a new version, like this long-read sequencing, scientists realize, "Gosh, there is so much more in this book of life. That genome, there's so much more we can now read." To some degree, it enables us to read better, like we get better with reading classes literally. Now, what's very important to understand is, "Okay, now we can read the book," but that doesn't mean we understand it. And understanding also has layers. Maybe I can sound out the words, but do I really understand the meaning of the words? Sometimes the sentences, they have a deeper meaning, right? It's the same in DNA. There's a deeper meaning, "Do we really understand this yet?" That's sort of where we struggle still.

Mindy Henderson: Interesting. Dr. Weihl, is there anything you would want to add to that?

Chris Weihl: I love that analogy. I guess the way I think about it is we used to have the book that we thought had all the words in it. And as Stephan said, technology evolves and we find that there were words there that we couldn't see until we put on a different set of glasses. And I think when we talk about these diseases, that 30 to 50% we can't find a diagnosis for, it's not that we haven't looked at the genes that we can read and have known that are there. It's likely that these diseases have genes or changes or rearrangements in the language that we haven't fully appreciated how to detect them yet. And I think that's the most exciting about next-generation sequencing, and then as Stephan said, long-read sequencing, is that it's allowing us to go back to that patient that may not have a genetic

diagnosis and revisit that patient with a new type of sequencing technology so that maybe we can identify a novel new gene, something that Stephan has made his career doing.

Mindy Henderson: Yeah. It's making me think of... I think every year, you hear new words that have been added to Webster's dictionary, and that's what you're saying is making me think of that translates for me. We talked about the difference between a clinical and a genetic diagnosis, and how they're interconnected and both importance in different ways. Can you talk about the impact that this technology has had, just a little bit more on people's diagnostic journeys and the ability to cut time down on the duration to get a diagnosis, and things like that?

Chris Weihl: Yeah. Go ahead, Angela.

Angela Lek: Yeah. No, I just wanted to jump in and just share my personal story. So when my husband was diagnosed with muscular dystrophy and we would see the neurologist every year or annual visits for 10 years, and they said, every year, "We don't know what's causing it. We don't know the gene that's defective. We don't know the root cause of your muscle wasting disease." That was very frustrating. So having that clinical diagnosis was great, but I felt like we needed more answers. Particularly for looking towards his future prognosis, therapeutic intervention, family planning, all those sorts of factors, it was really important that we had the answers, the genetic answers. So actually the reason why I took 10 years was because this was prior to the introduction of next-generation sequencing in clinical practice. They were doing it the old way, screening each gene one by one, and it was really painstaking. It took a very long time, and they couldn't find the offending gene.

But now, if he were to go to his neurologist now, or any new patient with his exact same disease, I imagine they'd get a diagnosis in just a matter of weeks using next-generation sequencing technology instead of waiting for a decade for answers. That's the power of the technology.

Mindy Henderson: I love that. Thank you for sharing that. And like you've talked about, there are new discoveries all the time that are happening. Is it a question of just working with your own personal neurologist, day to day, year to year, however frequently, to know when the time might be right? If they didn't have the right insight into what your genetic issue might be, how do you know when to test again?

Chris Weihl: Yeah. That's a great question, Mindy. I think it's something that... We probably, as clinicians, need to do a better job of letting patients know that if they don't have a diagnosis, we're always continuing to look for a diagnosis. So I tell patients who often come to the clinic and I can't give them a diagnosis today, I will usually look through and make sure that I've done everything or the previous doctor has done everything. I will try to understand their genetic tests that they had. And then often these panels increase, often you can escalate genetic testing to larger genome sets, often it may be that we need to try doing

a different type of sequencing, as Stephan said. Often it means reaching out to collaborators and saying, "I have this patient." Stephan has developed a network where, if I have a patient with CMT, I can give it to people that can aggregate things together.

So I think being at an MDA clinic is important. I think asking... it's a great question. I don't know if somewhat the clinician needs to be the one that kind of says, "Hey, I think we need to revisit your genetic testing." There's a new panel I can say from experience. Maybe 10 years ago, we did a very small genetic panel of maybe 30 genes. And the patient will hear they don't have a diagnoses, and then they will somehow drift away into the community. And then they'll come back to clinic 5, 10 years later and we'll be able to do a different panel that's expanded that might have 180 genes on it, and we will then identify a diagnosis. So one thing that pains me is to think that there are patients out there who could have a diagnosis but haven't reengaged with an MDA clinic or with a neurologist, or asked the question about, "Could this be a hereditary disorder?"

Angela Lek: Actually, can I jump in and say that all MDA care centers can send off patient sample to Invitae, the company that can run a testing panels for common disease-causing genes for neuromuscular conditions, and that's done... Invitae does that for us free of charge. And then should that not yield any answers, then as Stephan said, it then becomes a research project. And you can put on a different pair of reading glasses and look deeper using a different technology, such as exome sequencing or genome sequencing that both can give you more resolution to see if you can find the disease-causing gene that way.

Chris Weihl: I will say that neurologists, and even neuromuscular physicians, do not often get formal training in genetics. So having a genetic counselor in clinic with you or having someone that's comfortable with it. Because these panels, they only sequence what we know. So if I'm going to sequence 180 genes, I'm only going to look at those 180 genes. There are some things, in particular, in muscular dystrophies that are missed on those panels. One of them being facioscapulohumeral dystrophy, which would not be detected on a traditional panel and needs to be intentionally looked at other repeat disorders which need to be looked at intentionally. So I think that we need to do a good job of educating clinicians on knowing the limitation of the tests that they order, knowing what is on that test.

SMA, which can sometimes look like a limb-girdle muscular dystrophy, is not necessarily on some of the sequencing panels. It might be on Invitae. I don't know for sure. Becker muscular dystrophy, which can be found from a very small deletion, may not be picked up on some of the panels. So, again, your clinical suspicion needs to really drive the genetic testing, and so we need to go hand in hand.

Stephan Zuchner: Mindy, as Chris said, there's no strict guideline.

Mindy Henderson: Mm-hmm.

Stephan Zuchner: I would say from looking backwards, if you have a clinical diagnosis and your physician says, "That must be a genetic cause, but we can't find it yet," every five to seven years, if your insurance company agrees, it's probably worthwhile to revisit. If you're in a specific situation, maybe it's a child, it's growing, and you have this desire and panic to find an answer, then joining a research project isn't also a good idea.

Chris Weihl: Stephan brings up a good point. So it's not getting a genetic test every year. It's not going to one doctor getting a genetic test and then going to another, and hoping... It's really an evolution of years that needs to be aggregated.

Mindy Henderson: The other thing that's coming to mind for me is just the momentum that's being built in the research community right now and the progress that we've seen and that you've talked about today, and Dr. Zuchner, you mentioned clinical trials. How important is having an accurate genetic diagnosis to participating in a clinical trial, let's say?

Stephan Zuchner: Yeah. I would say it's increasingly fundamentally important. I sometimes use this picture of a coin. You have a coin that has two sites, right?

Mindy Henderson: Mm-hmm.

Stephan Zuchner: The genetic diagnosis, knowing what the gene is that doesn't work properly in you, is nowadays married to a potential for treatment. It would be great if there was sort of an aspirin or an ibuprofen type of drug like we have for pain, it covers all kinds of pain and fevers, and it would exist for neuropathies, for muscular dystrophy. People have tried and they still try to find this kind of aspirin for muscular dystrophy. But so far, it's not being super successful. So what the medicine is now looking, and Chris mentioned already, is gene-specific therapies. Drugs that target a particular gene, sometimes even a particular mutation. Of course, you can only do this when you know the gene that you carry. In fact, I've seen many stories over the years. Sometimes there is somewhat lucky situation where we find a new gene and then we realize, "Oh." We basically look around and say, "Oh my gosh."" All these patients around, we find like a dozen and more patients right away that have this new gene that was there all the time.

And then, luckily, it turns out we understand this gene actually quite well. There is even a drug that looks promising that maybe was developed for another disease, sometimes even for cancer or something. And it's very obvious to scientists that this drug might actually work. So in some fortunate situations, it has happened that suddenly there was a great drug candidate. But again, it all happened with the discovery of the gene and the diagnosis in these particular patients. And that allows then these patients to participate in clinical trials, for instance. I mean, Angela, that's at the heart of much of what the MDA is doing

these days is pushing this message. That's sort of gene-centric approach to diagnosis, of course, to future therapies, trials, all of that.

Angela Lek: Yeah. A lot of the trials that are emerging are utilizing gene replacement technologies, RNA-targeted therapies, even now, gene editing. And all that requires a genetic diagnosis, knowing exactly which gene is causing your disease and the type of mutation that's causing that effect.

Chris Weihl: This is why it's so critical for patients if they get a genetic diagnosis. So first off, to hear about a therapy, the therapy is going to be for one related neuropathy. Patients are going to need to know that they have a mutation in that gene. I don't expect patients to know that. What I do want patients to do is to feel empowered to ask their clinician for their genetic test results, put it in a file somewhere. Even if it's in negative genetic test result, hold onto it because invariably patients come back to me and say, "Hey, I've already had genetic testing." "I don't actually know what that means. We just talked about that." So if they have their genetic test result, it's helpful.

As Angela said, it's not just going to be gene-specific therapies, it may be mutation-specific therapy. So you may tell me you have a mutation in dystrophin, but I have a therapy that's only amenable if it's Exon 45 skippable, that's only going to be on your genetic test result. So this needs to be people's new social security card that they hold onto and have because, as we heard, the journey to get the diagnosis took years. And if you have that diagnosis, keep it in a piece of paper and put it somewhere so that whenever... The expectation that I'm going to be able to find it in the medical record is really hard. There's no tab for genetics-

Angela Lek: Put it in your wallet. Carry it with you.

Mindy Henderson: Have it laminated. Exactly. So what would you all say are still the biggest challenges that remain in terms of getting diagnoses to people, and how are researchers working to address those gaps that still exist and maybe among the biggest?

Stephan Zuchner: I guess, there are two categories. One is challenges around how healthcare is working in our country, and the other is the more scientific challenge. And maybe I can talk about the scientific challenge. Chris, I'm sure is happy, or Angela, to talk about our healthcare system. For me, it's the scientific point of view. We just made it very clear how important it is to know your gene if you have a neuromuscular disorder. And it drives me personally, the realization, that so many patients that it still don't know their gene. If you know, it opens a whole set of doors for you once you know it. So the challenges for knowing your gene from a scientific point of view is often related to... there are more genes to be discovered. Or maybe a new sequence technology gives us new reading classes and, suddenly, we understand the meaning of parts of the genome. Okay?

Mindy Henderson: Mm-hmm.

Stephan Zuchner: That's sort of what we are trying to tackle with different approaches. One thing that's close to my heart for a long time is... When I started my career, the way to do this type of research was to find patients that had many family members that were still available to study. And these families with multiple affected individuals, they were sort of almost the only way to get to the core of the genetics. So we would study these families, everybody would study these families. And if you had just a handful of these families, you actually had somewhat the power to find a new gene. In some ways, most of these families have been studied. But there are other ways to do it. So the way today to do it is, even very small families where maybe only one or two people are affected, to bring them together into a research database. And when you put them all together, you also gain the power to understand what's wrong with certain sets of individuals and patients.

So the core here is that scientists collaborate with each other, in the United States, but also internationally. And this has wonderfully developed over the years also to share the data. It's very important also to hang on to data that's already been produced. That sounds maybe obvious, but a genome is a very large dataset. It's like 20 Netflix movies. Okay? That's one genome. So it's hard to hold onto that kind of data. So to do that and to share all that continues the momentum that we find these missing genes that we still haven't discovered, so that more patients get into this situation where they can then go to Angela and say, "Here, this is my gene, MDA. What is the next step?"

Mindy Henderson: I like that idea.

Chris Weihl: I would say another challenge we have... I totally agree, identifying new genes and identifying those in the patients. But I would say, clinically, another challenge we have are indeterminate genetic test results. These are genetic test results where the geneticist has identified them as something called a variant of unknown significance, or perhaps they have a variation in only one gene and not on the second gene. I think these can be just as equally frustrating to a patient because they're left in this area of limbo. And sometimes it takes a little bit more legwork. So it may require doing a muscle biopsy on the patient. It may require sequencing a family member in order to help kind of understand, "Did that little variation in that patient truly means something pathogenic?" And the other way is exactly what Stephan said, which is collaborating and building a network so that we can understand, "This variation that's found in this one patient, is it also found in another patient? Or is it found in a patient..."

Whenever we start thinking about patients, I think we need to be thinking not just about patients in our local community, not just patients regionally or in the US, but we need to be thinking about patients globally. We need to think about sequencing in under-represented areas, in areas that we don't often have the breadth of genetic diversity from, and that will continue to inform us about, "Is a sequence variation causal or is it perhaps something incidental?" And I would

say identifying a incidental variation is equally important because that means we need to start looking again and seeing if we can find the real cause.

Mindy Henderson: So interesting. I have time for about two more questions. I could talk to you all day, you're all so interesting. But Dr. Lek, let me ask you, what types of research and initiatives have MDA supported over the years to help overcome the kinds of challenges that we're hearing described so that we can get more and more patients answers?

Angela Lek: Yeah. Look, Mindy, we've funded several efforts as it relates to helping patients obtain a genetic diagnosis, to better understand genetic variants that lead to disease, and to discover new disease genes, as Stephan talked about. For example, we funded Doctors Lowell and Todd from NIH to develop a comprehensive database to link genetic mutations in the ryanodine receptor gene with specific clinical features, in order to get a better understanding of the spectrum of disease-causing mutations and how they can cause disease-related symptoms associated with this calcium channel disease, so to begin cataloging each of the mutations that's seen in patient cohorts. MDA has also funded my better half, Dr. Lek from Yale University, to develop cell-based assays to predict the pathogenicity that is, "How likely a genetic variant or mutation is to cause a disease?" And this approach was applied to a subtype of limb-girdle muscular dystrophy in an attempt to shed resolution on the variants of unknown significance in the FKRP gene, something that Chris touched on.

This method is also now being expanded to interpret mutations or variants in the sarcoglycan genes that give rise to a few other different types of limb-girdle muscular dystrophy. And I believe Dr. Weihl is also doing some of that research and contributing efforts to that. Finally, MDA has also contributed funding to Dr. Zuchner's Genesis platform, which is a platform for genomics data management comparison and analysis, that gives researchers the tools they need to help families with their diagnostic journeys. I believe the Genesis platform has supported over 100 gene discoveries, and this is so powerful in helping to end the diagnostic odyssey for some families that have been struggling to get a genetic diagnosis for years.

Mindy Henderson: It's amazing to listen to all of you, and to hear you talk about the different areas and factors. It feels like we should know all the answers to listen to you. It feels like we know so much, but I know that there is still a lot that we don't know. And as for someone speaking who lives with one of these neuromuscular conditions, if there's not a way to make a condition like spinal muscular atrophy or Duchenne dystrophy, or any of these neuromuscular conditions that we're talking about, if there's not a way to turn that into just a bad dream that you can wake up from, the next best thing I think is to uncover the treatments of the therapies that are going to lighten the load a little bit on what these conditions do to your body. So I'd love to give each of you the opportunity to answer this question and talk a little bit about the use of next-generation sequencing and how it's opening new doors for therapies to expand more and more possibilities

for research. And ultimately, what we all want is, "Which are the therapies to treat these conditions?"

Chris Weihl: Right. I can start, I guess?

Mindy Henderson: Mm-hmm.

Chris Weihl: I think what we don't realize is we just don't know the prevalence of many of these disorders. And when I say that, we don't know how many patients with a mutation in calpain-3, for example, are out in our communities. So I think that next-gen sequencing, which has allowed easy, rapid genetic testing, has allowed us to bring patients together. And I think by bringing patients together, we then can create power of these patients to create patient communities to then lobby to interest groups, whether that's drug companies, whether that's the government, whether that's the MDA and say, "Hey, we're not this rare disease. We're this rare disease that is well organized, well connected. And we're looking for more patients because we're able to do genetic testing so easily."

So I think that's been really powerful, is just allowing the identification of more and more patients with what we call rare diseases in our rare diseases. But whenever you can bring them together because of a genetic diagnosis across the country, I think that ends up being really, really powerful. So I would say next-gen sequencing has allowed me to do genetic testing in the clinic without having to ask insurance companies, without having to go through a lot of leg work, and then give the patient the answer and allow the patient then to use that to empower themselves and their patient community.

Mindy Henderson: That's great. Dr. Zuchner, what are your thoughts?

Stephan Zuchner: Yeah. All of this, and I'll give you a bit more of the sort of basic science taste here. I think what next-generation sequencing really has changed is... We used to print things out and have it in paper files. And this technology, when it started some 20 years ago, made everything digital. I've seen in the last decade, genetics has become very much a data field, a computational field. It has attracted mathematicians and engineers. And now the latest, of course, it's probably quite amenable to AI. I think we will see breakthroughs from AI. It's already been used to help us understand what this all means. So the transformation of this field to this digital powerhouse is still underway, and it's one of the most fascinating things to see.

Mindy Henderson: Amazing. Dr. Lek, I'll give you the last word.

Angela Lek: Sure.

Mindy Henderson: What would you like to leave us with?

Angela Lek: Well, look, next-generation sequencing really creates the foundation for targeted treatments, I think, that can be tailored to patient's genetic profiles. Once the genetic cause is known, therapies can be tailored to the specific mutations. So for instance, antisense oligonucleotides that correct RNA splicing, gene replacement therapies for loss of function mutations, or even gene editing to correct a range of mutation types. Next-generation sequencing has really opened the door for genetic medicine. I want to share one of the most powerful examples of what's possible in genetic medicine, and it's the story of baby KJ. I don't know if you've been following that or read about that in the news. Baby KJ was born with a life-threatening metabolic disorder caused by a unique genetic mutation. And using rapid genome sequencing or next-generation sequencing to pinpoint the exact defect, scientists were then able to design and deliver a custom gene-editing therapy using CRISPR technology specifically for him just six months later.

This case really showed what's possible, to go from a genetic diagnosis to a bespoke genetic medicine treatment in just a matter of months. And most importantly, that it could be applied to newborns who have a life-threatening genetic condition to give them a fighting chance. This has become a landmark moment for personalized therapies, genetic medicine, and also showcases the advancement of next-generation sequencing technology to obtain that rapid genetic diagnosis that enables all of this in the first place. And hopefully, this can one day translate to life-threatening neuromuscular conditions diagnosed at birth.

Mindy Henderson: That's incredible. That gave me goosebumps. Thank you for sharing that. It feels like there's so much to be hopeful about, and I have thoroughly enjoyed speaking with all of you today. I can't thank you enough for your time. Honestly, I want to take the opportunity just to thank you for the work that you do every day. Because knowing that you all are behind the scenes, working on solving these problems, is what allows the rest of the community to live every day with the hope that things will change. So thank you.

Chris Weihl: Thank you, Mindy.

Angela Lek: Thank you.

Stephan Zuchner: Thank you.

Mindy Henderson: Thank you for listening. For more information about the guests you heard from today, go check them out at mda.org/podcast. And to learn more about the Muscular Dystrophy Association, the services we provide, how you can get involved, and to subscribe to Quest magazine or to Quest newsletter, please go to mda.org/quest. If you enjoyed this episode, we'd be grateful if you'd leave a review. Go ahead and hit that subscribe button, so we can keep bringing you great content. And maybe share it with a friend or two. Thanks everyone. Until next time, "Go be the light we all need in this world."