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Episode 27: The Changing Landscape of Neuromuscular Care March 10, 2023

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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.

I am so excited to tell you that our guest today is Dr. Matthew Harms. Dr. Harms is a neuromuscular neurologist and neurogenetics expert focused on ALS and related motor neuron diseases. He is the director of Precision Medicine Initiatives at Columbia University, director of the Neurogenetics Program in the Department of Neurology and associate director of the Eleanor and Lou Gehrig ALS Center. Dr. Harms also serves as a medical advisor to the MDA. Dr. Harms, thank you so much for being here.

Dr. Matthew Har...: Well, thank you for having me. It's always a pleasure.

Mindy Henderson: Thank you. Your expertise is clearly vast and we are so lucky to have you here today and there's a lot to talk about, so I'm just going to jump right in if that's okay.

Dr. Matthew Har...: Absolutely.

Mindy Henderson: Sounds good. Well, would you mind telling us a little more about your career as a neurologist and when you started to focus on neuromuscular disease?

Dr. Matthew Har...: Yeah, absolutely. So I first got interested in the nervous system in high school biology. I guess that was one of the small sections where I was actually paying attention and was fascinated to hear that electrical signals went through these things called neurons, and that those electrical signals turned into chemical signals, and then the chemical signals were translated back into more electrical. I mean, it was just mind-boggling the way that our nervous system interacted with our brains and our muscles to get things done. So when I got to college, I was very heavily focused on neuroscience and knew that I would head off to medical school and ultimately onto neurology residency.

But in neurology residency, I learned that the vast nervous system was fascinating from one end to the other, that you had to subspecialize, that each subspecialty took on roles for different things. So autoimmune diseases like multiple sclerosis were taken care of by one group of people, vascular diseases by another group of neurologists, and there were developmental diseases. Basically just plethora of these different things to get excited about. And honestly, initially in residency, I loved all of them, but by my second or third year of residency, I really found myself fascinated, again, going back to my first love and interest in biology to these nerves and muscles and how they produced strength and sensation and those things. And so, I decided to become a neuromuscular neurologist.

Mindy Henderson: Wonderful. Well, let's talk about your role as a medical advisor to MDA. What led you to working with MDA?

Dr. Matthew Har...: Yeah, absolutely. So I was fortunate enough to do my neuromuscular fellowship at Washington University in St. Louis, which is one of the largest Muscular Dystrophy Association care centers and one of the nation's top destinations for these types of diseases. And so, I had physicians that trained me for the entire spectrum of neuromuscular disease, beginning in infancy, all the way up into the later stages of life. And that very broad exposure is a patient population that the MDA serves. So I worked very closely with the Muscular Dystrophy Association in clinic and then have an especially soft spot for them because they actually gave me my first invitation to speak at a conference where I introduced a new topic to people called next generation sequencing. The type of genetic testing that everybody gets these days was just in its infancy, and I

happened to be working on it in the lab, so I presented about it at the conference. So I've had the privilege of basically having the MDA be a part of my professional and personal development basically since I first became a neuromuscular neurologist.

Mindy Henderson: Oh, that's fantastic. Nice. And you and I were talking a little bit, we were chit-chatting before we began the interview, and I know that you're actually going to be at this year's scientific and research conference that MDA puts on every year in just a couple of weeks here in Dallas, Texas.

Dr. Matthew Har...: Yeah, I'm very excited about that, to be in Dallas for four or five days. I'll be leading a series of presentations about ALS and the developments of genetic therapies for that disorder. And then helping people at MDA care centers that take care of patients with ALS anticipate how our clinics are going to need to change and adapt when we have a therapy like that that's very successful but also very intensive and potentially difficult to administer.

Mindy Henderson: Absolutely. Well, I will look forward to hearing you speak. So tell me a little bit more about what it means to be a medical advisor to MDA. What does that role look like?

Dr. Matthew Har...: Absolutely. So first of all, it's lots of fun. I get to work with the incredible directing and leadership teams at the MDA who are really thoughtful people but aren't necessarily physicians and aren't spending most of their days in MDA care centers kind of on the front lines. And so, a typical question will be, how do we structure camps so that it's as safest possible from a COVID perspective? How do we take the donations and steward them as best as possible to make sure that they're being equally distributed? What should we invest in in terms of the care center and infrastructures? How should we manage the grants? What are you anticipating will be the major changes, and how care needs to be provided five years from now to help horizon set for what do we do and how do we reorganize when we have super effective therapies for this disease or that disease? So all sorts of great questions. The leadership of the MDA is asking all the right questions and really leading well to make sure that the organization and its care centers are positioned for the future, not just what's happening today.

Mindy Henderson: That's great to hear. And we love our medical advisory board, I know that it's a critical role that you play. So do you spend more of your time today seeing patients or is most of your time focused on research?

Dr. Matthew Har...: It's probably 50/50 split right now. So my career, it ebbs and flows and how much I'm in the clinic versus the laboratory, but right now it's about 50/50. So I'll be seeing patients many days out of the week, both in the pediatric muscular dystrophy care center and then the ALS care center. And then the rest of the time, I spend my working on questions around genetics and genomics, organizing committees to make sure that we get the information out about the individual genes that we know a lot about, that we focus in on sequencing for the genes we don't know a lot about. Also, trying to work with companies that are developing genetic therapies, trying to help them figure out which mutations will respond to the therapy that they're working on, which types of patients should be included in clinical trials and which ones shouldn't. Answering those types of questions from a research perspective.

Mindy Henderson: That's great. And I'm so lucky to have a doctor and a researcher here at the same time, and I've got questions around both patient care and research. So buckle your seatbelt.

Dr. Matthew Har...: Great.

Mindy Henderson: Can you tell us a little bit more about your research and what's been the most exciting to you? So much has changed in neuromuscular disease medicine, what's been the most exciting for you as a researcher in recent years?

Dr. Matthew Har...: So it used to be the case that people would come to the care center and get a really general diagnosis. We would say, "You have a muscular dystrophy of some type." Then when the low cost sequencing that I first was describing to people at that muscular dystrophy conference all the way back in 2007, 2008, something like that, now in the majority of patients, were able to zero in not just on the gene that the culprit, but the specific type of mutation. So there was a phase where we could then tell people about the specific mutation and how we thought it might be causing a problem. And now we're in this phase where we have some molecular tools, some gene therapy type tools where we, in some diseases, are already manipulating the genes based on the mutations and then a whole host where we're on the verge of being able to do that. And so I think that's been the biggest change that's taken place.

And I think one of the things that I think has allowed that to occur is that geneticists and neuromuscular doctors have been working closely together for a long time, but maybe not all around the world. And so, now we have these research consortia that basically if I

find a candidate gene and somebody here in the US, I can immediately find half a dozen, a dozen, sometimes two dozen collaborators around the world by looking in databases for these same genetic problems. So it's really sped up the amount of time so we can discover genes faster. And then of course the discovery of a gene is just the beginning because then we need to know, how does the gene work, what's wrong with the mutated gene, and how can we repair that? Can we replace the gene? Do we need to actually delete the gene by blocking its use? Do we need to compensate for the genes function with a small molecule or a therapy of some type?

Mindy Henderson: And so, everything that you're talking about is it's incredible, it's amazing how far the field has come. What does this all mean for the neuromuscular disease community and the patients in that community?

Dr. Matthew Har...: So for our most common diseases, it means either we have FDA approved molecular therapies that are increasingly effective or are on the verge of having molecular therapies, hopefully, based on FDA action coming up here. But I think that for the broader community where we don't yet have those molecular therapies, the good news is that the things that are being learned in these more common diseases with these same types of molecular therapies are going to translate into quicker development, safer development, more effective development for the more rare forms of genetic neuromuscular disease. So if it's not your particular gene or your particular genetic problem where you're seeing all of the movement, the lessons that are being learned by the companies developing those medications and the clinical trialists running the clinical trials for those are going to allow for a more quick dispersion of those technologies into the rarer diseases as we get better at doing it and faster at doing it and more comfortable, and the FDA gets more comfortable with less data and fewer patients and the clinical trials and what have you.

So I think it can be hard if it's not your particular neuromuscular disease where you're seeing all of the movement wondering like, "Why not my gene, why not my specific disease?" But I think the silver lining, if that's the case for you, is that these same technologies, the same lessons that are being learned, the same safety data that we're collecting and these more common neuromuscular diseases will soon be translatable very quickly into the rarer forms.

Mindy Henderson: That's great. And speaking of those treatments, as a neurologist treating patients with neuromuscular disease, I'm not quite sure what the first actual therapy or treatment was that was approved in this space. But I'm wondering, can you remember the first time that you were able to prescribe one of these treatments, Spinraza or Exondys to one of your patients?

Dr. Matthew Har...: Yeah. So let me back up for just one second. When I was trying to decide what to do with my neurology career, a wise many years senior clinician said to me, "One of the nice things about neuromuscular medicine is that it's even split between patients with autoimmune neuromuscular diseases like myasthenia gravis, CIDP, and autoimmune muscle like myositis, where you can intervene with medications that we already have today, make a huge difference and improve their strength, and then the genetic diseases which are intellectually interesting and need researchers to basically tackle." So he was basically pitching this even split. So there were people you could fix and heal today, and then people you could dig your research teeth into and intellectually approach for the future.

And so, I think one of the things that feels amazing about encountering a patient with myasthenia gravis is prescribing IVIG and watching their symptoms melt away over the course of three or four weeks. And so, to be able to envision doing something like that in spinal muscular atrophy, Duchenne muscular dystrophy with these genetic therapies wasn't even in my thinking when I first started. But now, of course, we have some of those therapies. They don't work as well as IVIG in myasthenia, but we're getting there and they make a huge difference. And so, I think that's been my experience and it was really exciting to be able to think about disease modifying therapies.

Now Columbia and the Children's Hospital of New York or CHONY, as we call it here, is a major destination for spinal muscular atrophy research. And so, we've been taking care of kids in clinical trials on Spinraza or nusinersen for quite a number of years before the FDA had approved it. And so, once it finally got approved, was a huge relief to everyone in our center because we couldn't get it for everyone. Kids that didn't meet inclusion criteria for the clinical trials didn't have it as an option, and yet we knew from our firsthand experiences that it was working, that it was making a big difference. And so, I think there was just a huge relief when it was approved so that we could then supply it to as many kids as needed it.

Mindy Henderson: That's amazing. And I will just share on a personal note that I personally live with spinal muscular atrophy and have had the benefit of getting access to Spinraza for about four years now, and it's been a life-changing experience.

Dr. Matthew Har...: Yeah, amazing.

Mindy Henderson: Yes. So there are all sorts of exciting and interesting technologies emerging in neuromuscular medicine. We hear about CRISPR, gene therapy, ASOs. One of the things that we are seeing is that, to your point, when find a technology that works for one condition, sometimes it can then be leveraged to treat other conditions down the road. In neuromuscular medicine, there's so many variations of different diseases and things like CMT comes to mind, and so many of the conditions that just within a condition itself, there are so many different forms and types and variations. How does that complicate research and the ability to put therapies into people's hands?

Dr. Matthew Har...: Yeah. So you're right. So we call that genetic heterogeneity, which just means that the genes and the types of mutations are very heterogeneous, differing often from one person to another. And even within the same gene, the specific mutation might have very different effects. There are some that are super severe, some that are super mild, some where you need two bad copies instead of just one bad copy, and it does make it complicated but not intractable. So we now have the technologies, of course, to figure out what the specific mutations are and are learning more about how those specific mutations cause the disease. Is it a situation where the genetic mutation hyperactivates the gene, in which case you would need to turn it off or turn it down to treat it? Is it the type of mutation that causes the protein to be completely missing, and so you actually need to completely replace it or put in something that does a similar job, in which case you have to supply it?

And then in some circumstances, it's more complicated than that and you need to shift the cell from using the whole gene to using a better part of the gene or prevent it from misusing part of the gene. So you're right, it's gotten very complicated. The good news about it getting complicated is that means we're understanding it. Before, it was just a black box and we were like, "Oh, this is CMT type 2Z," or whatever we're up to now with the initials. But now we can really start to understand those molecular underpinnings and then start to apply the specific molecular tools to try to go in the other direction to reverse the problem.

And the good news is that while we're treating these more common diseases, we're getting everybody more comfortable with the safety of these different technologies to the point where, at some point in the future, we'll have personalized therapies that the FDA would allow, where you might be in a family that has a specific mutation, and we know that it's hyperactivating, and so we need to shut off that gene with an ASO, and that ASO might be custom designed to only work to shut off your version of the gene, your specific mutation.

We're already doing some of that in ALS, a program that's being run by one of my colleagues here at Columbia called Silence ALS is working to develop what are called allele-specific antisense oligonucleotides, where they are designed to shut off one bad version of the gene to try to slow the rate of progression in ALS. And the costs and ability to do that are getting cheaper. And as the FDA gets more comfortable with very limited safety data coming from a handful of animal models and then just a handful of patients, we'll get there, to the place where personalized drugs are available for these very rare and even unique individual mutations. I think the other thing I would say is that it's not just the therapy and tools that we have today can be turned around quickly and leveraged for other diseases, it's also the fact that it's opened up people's minds to the what's possible, right?

Mindy Henderson: Yes.

Dr. Matthew Har...: People might have said, "It's impossible to do this. It's impossible to fix the genes. Gene therapy is impossible." And then you have a couple of big noticeable successes, and suddenly companies have opened their minds. And so, not only are we seeing repurposing of the same molecular technologies for different diseases, but we're also seeing a lot of innovation into new types of molecular therapies. New companies coming into the space, coming into neuromuscular disease, excited by what they've seen with ASOS and AAV like, "What's the next generation of that? Let's bring that to neuromuscular disease." So lots of new biotech startups and pharmaceutical companies investing in neuromuscular disease that didn't before, that were nervous about doing it before, but the fact that it's turned out to be some of these diseases are treatable, has gotten everyone excited and is bringing people into that space.

Mindy Henderson: So true. I think it really brings about a lot of hope for the patients and the families that are part of this community. Let's talk about the diagnostic journey for patients with neuromuscular disease for just a second, because just getting a diagnosis can be very tricky. And I

know that that landscape has changed a lot over the years. Back when I was diagnosed in 1975, they diagnosed me ultimately with a muscle biopsy. And so, can you talk to me a little bit about how just diagnosis of neuromuscular conditions has changed?

Dr. Matthew Har...: Sure. Absolutely. So it's really literally been flipped on its head. The order in which people undergo testing has been completely transformed by genetic sequencing. You were diagnosed in an era where we didn't know the genetic explanation, but we could recognize the clinical symptoms and what it did to muscle and be able to say, "Okay, this is spinal muscular atrophy because we see these very big muscle fibers right next to little tiny muscle fibers." And when we see that, we know it's spinal muscular atrophy or something like that. And then it got to the point where we knew where the gene was located on chromosome 5q, but didn't know what exactly was going wrong there, and then to the era where you could detect the absence of the SMN-1 gene. But that took a long time, and at first, it was an extraordinarily expensive test that was cost-prohibitive.

So the same has been true for all neuromuscular diseases. Even once we've found the gene, it would be very expensive to do the sequencing to figure out and confirm your suspicions. So you would do muscle biopsies and staining of the muscle, sometimes a second muscle biopsy, basically invasive testing. Nowadays, you basically recognize the pattern and then you go straight to the genetic sequencing because you can skip many of the invasive steps. Sometimes even an EMG nerve conduction study, which is a mainstay of deciding whether it's a nerve problem or a muscle problem or which cells are involved. So I think more and more patients are getting firm diagnoses much earlier in the disease process. There's still room to improve on that. There's people who don't realize how easily genetic sequencing is available, how much the cost has fallen.

There's still a perception that it's an extraordinarily expensive test or that insurance companies don't cover it. And there are circumstances where that's the case, but that's not the rule anymore. And so, we definitely want people to be able to get a molecular explanation. And the reason for that is several fold. One is that as good as we are, as diagnosticians and clinicians, sometimes we're wrong. Sometimes somebody looks like they have a muscular dystrophy, and when we do the sequencing, we discover that they actually have a very mild form, not an SMN1 type of spinal muscular atrophy, but a different gene causing something like spinal muscular atrophy. But it creates weakness in all of the

same places as somebody with limb-girdle muscular dystrophy. So sometimes we learn that we're in the wrong category altogether when we were thinking about the person's disease.

Getting a molecular diagnosis also opens up the possibility of learning from other people with that same gene or that same mutation to have a better understanding of what might be down the line in the future, or does the heart get involved, do the lungs typically get involved, things that we need to know to provide great care, and then to know which research to pay attention to. So once you have a genetic diagnosis, then you can look in Quest and Google search for that specific gene to see who's doing research on it, what are they learning, what are the gene specific things that are coming out that would be potentially applicable to your disease. So I think the diagnostic odyssey is much shorter, it comes to an answer for more and more patients. And then I think that diagnostic odyssey used used to get the diagnosis, and that was the end of the diagnostic odyssey.

Now, the end of the diagnostic odyssey is actually just the beginning of the therapy odyssey, which is what's currently available, if anything? Who's working on the next generation of things that are going to be more effective? And how do I get connected to that community? Is there a natural history study where people are preparing for clinical trials by studying the people who have the disease now? So that when a treatment is available, we're ready to go, we know how fast things progress, we know which biomarkers change, we know what the pattern of muscle involvement is, so that when we do have a therapy to test, we know what we're doing and how to run those clinical trials more effectively.

Mindy Henderson: So interesting. And so, when someone comes into your office and they're presenting with certain kinds of symptoms and things, do you, at that point, have a pretty good suspicion of what the possibilities might be for them? What's the first step that you would take based on just the symptoms someone's having?

Dr. Matthew Har...: Absolutely. So we're still neurologists, and the very first thing that a neurologist has as their goal is to use history and physical examination to try to figure out, where in the nervous system the problem is localized? Is this an issue coming from the brain? Is it coming from the spinal cord? Is it coming from the nerves? If it's a nerve, is it just the motor nerve or just the sensory nerve or both? Is it the connection between the nerve and the muscle, or is it the muscle? So because most genetic explanations tend to affect one

of those different levels, you got to have a great instinct idea from the history and the physical exam, which genes are possible so that you order the right test? And more importantly, I mean, you could order all of the genes in the whole genome, people are doing that these days, but then you have to be able to interpret it.

So if I see a patient and I'm convinced that they have a muscle disease, but somebody finds an abnormality and a nerve gene and it's kind of uncertain significance, I'm going to know, "Hey, that's probably unlikely to be the explanation. We need to keep looking harder for a muscle disease gene, because I'm confident from my exam and what I did in the clinic that this is a muscle disease. So we'll start there." So I think yes, when someone comes in the clinic, pretty quickly after that first visit, maybe with an EMG nerve conduction study, if you need more clarity, if you have a good sense of what's going on, and then you pursue the next step, which is almost always genetic testing, maybe in parallel with some other things, MRIs, EMGs. We still do biopsies, they still can be very helpful. Especially as more and more people get sequenced, we're finding genetic differences, and I call them differences because we don't know whether they're genetic mutations, they could be abnormalities, but they also might just be the differences that make us all human and different from one another.

And so, it's not uncommon that we do a big sequencing job and we get three or four possible things that could be the explanation. And then you often have to go back to the muscle and look at it and ask the question, "Okay, we saw this abnormality in the Duchenne gene. Let's go stain the muscle for the Duchenne protein and see if it's normal or abnormal. Okay, it's normal. That means what we saw in the Duchenne gene is not the culprit, that's just a difference in that person. Okay. What about the difference that we saw in ANO5? Okay, well, let's go look if we see the differences that we associate with ANO5." And so we don't get everybody out of their biopsies, out of the more invasive testing, but the genetic testing does help avoid quite a bit of it.

Mindy Henderson: It's fascinating. And I want to throw one more sort of wrinkle into this for you and get your thoughts in terms of diagnosing conditions. With your deep roots in ALS, I know that ALS can be a condition that's particularly difficult to diagnose, and it's a condition that can have genetic factors, or it can be a spontaneous occurrence of the conditions. So how does that complicate things? How does that type of scenario make it harder or not for your job?

Dr. Matthew Har...: Yeah. So ALS can be difficult to diagnose when it's early. By the time it really gets rolling, unfortunately, it becomes pretty apparent very quickly for most people. So the average person gets into clinic around the nine month or the one-year mark. We're working very hard to try to decrease that. And the ways that we're doing that is to get the word out there about ALS to raise awareness, but specifically to do it in the non-neurologist's office where patients often present. So a common way for ALS to present is with weakness and atrophy in the hands. And there's a specific predilection for this big muscle here, which is the same muscle that gets atrophied with carpal tunnel.

And so, it's not uncommon for ALS patient to, first, get diagnosed with carpal tunnel, be seen by an orthopedic surgeon, have surgery on their carpal tunnel, they're not getting better with their rehabilitation after their carpal tunnel surgery, and it seems to be spreading, and then for it to be recognized that it's ALS and sent to the neurologist, or to develop ankle weakness and it looks like a pinched nerve in the back or to have slurred speech and for somebody to spend a lot of time at the ear, nose and throat doctor trying to figure out why their tongue isn't working as well as it's supposed to. So those are the groups of doctors that we're targeting to help them recognize the signs of ALS earlier so that diagnoses can be made earlier. That's even more important now because we're on the verge of potentially having gene therapy for the small group of people who have genetic mutations in ALS genes. So right now, whether you have a family history of ALS or not, there's a 12% to 15% chance of finding a genetic mutation in one of the known ALS genes in ALS.

And one of the more common genes, the SOD1 gene now has a molecular therapy going before the FDA for approval. We'll probably hear in April whether that gets approved. And there are clinical trials for three other genes that cause ALS. So we need to do a better job as a medical field of finding people with ALS earlier, I mean obviously, so that they can get an accurate diagnosis early and the therapies that we know slowed the disease down early, but also so that we can get genetic testing done early so that if they do have a mutation, we can get them access to clinical trials or to potentially FDA approved medications for those genetic mutations.

Mindy Henderson: So good. I could do this all day. You're so interesting to talk to. Let's talk a little bit about newborn screening. This is something that I am fairly passionate about. Newborn screening wasn't available when I was an infant. And in my mind, the earlier you can catch a condition like this and begin to treat it and deal with it the right way, the

better. Tell me about the effects that you're seeing on this area of medicine.

Dr. Matthew Har...: Absolutely. In particular, in spinal muscular atrophy, newborn screening has made a tremendous difference. Really, by the time an infant is one or two weeks old, we know that there might be spinal muscular atrophy and can intervene with gene therapy followed by splicing therapy like nusinersen or a risdiplam. And we have a sense, and I think the data is coming soon to prove that the earlier, the better. That's just very clear. I think that's true for all neuromuscular disease. I think this makes intuitive sense. If you can prevent the deterioration from occurring, prevent the degeneration from occurring is going to be a much easier thing to do than stopping it once it's gotten started and is kind of the runaway freight train.

So newborn screening is great in that respect. I think depending on where you live, the newborn screening panels differ. Here in New York, we have a newborn screening for acid maltase deficiency, also known as Pompe's disease. And one of the things that I love about clinic now is that I'm following a group of young kids who have been found to have mutations in their acid maltase gene that are predicted to go on to cause acid maltase deficiency myopathy at some point in their future, but we don't know when. And so we follow them very closely looking for the very first signs of muscles, not coping well with glycogen storage so that we can then intervene with the enzyme therapy to basically undo it before that damage takes place and causes the muscle fibers to degenerate.

Mindy Henderson: Wow.

Dr. Matthew Har...: As excited as I am by the newborn screening, I'm also encouraged by all of the prenatal testing that's taking place amongst young parents, people who are interested in starting families who are, through their obstetricians, learning in advance what the possible diseases are that could pop up as they have kids. And reproductive technologies are another avenue for preventing disease from taking root. There are now ways to do pre-implantation genetic testing and ways to kind of plan your way out of having a really difficult neuromuscular disease resulting from the genetics. So genetics is helping out on all fronts, it's helping people who are already symptomatic by coming up with an explanation and potentially suggesting a therapy, it's helping folks at the very earliest stages of the disease or even before the disease kicks in through newborn screening, and then even helping further back preventing the

disease from occurring by enabling people to do pre-implantation genetic testing.

Mindy Henderson: That's amazing. I mean, honestly, in my mind, anything that we can do that's of a preventative nature is incredible, and they're always, not always, but they're slowly adding additional conditions to the panels and all of that. And I'm just really excited to see this get more and more robust.

Dr. Matthew Har...: Well, one thing that's very encouraging, we've been told by several genetic sequencing companies that the \$100 genome is right around the corner, maybe even coming out this year. So you can imagine that if we could get our act together as a society to put genetic protections in place, to protect people's privacy, to make sure that people don't get discriminated against because of gene mutations that are found that might have implications later in life, that you can envision a world where basically every genetic condition gets screened for because, at birth, people are having their whole genome sequenced. And that information used to predict which diseases neuromuscular and otherwise might be down the road. Lots of ethical things to talk about there and safeguards need to be put in place, but newborn screening I think will be that comprehensive in the years to come.

Mindy Henderson: That's incredible. I have one more question for you, and then I just want to ask you a few questions about patient care. But we hear a lot about MDA's MOVR system and other registries like the ALS Registry. How do these things play into neuromuscular medicine today and why is it important for patients to potentially participate in those registries?

Dr. Matthew Har...: Yeah, absolutely. The MOVR Hub and other databases, what we call genetically informed natural history studies are an essential component of designing clinical trials for patients with rare neuromuscular disease. You need to know, how fast do things change for people untreated? How do the interventions that we do in clinic alter that so that you can plan how long does a clinical trial need to be? How many people do you need in order to see a 50% effect? Which genetic mutations progress faster, maybe too fast to treat in the first round of clinical trials, or maybe your drug is likely to work on a specific gene mutation? How do those gene mutations affect how fast someone's disease changes or which organ systems are involved? So these natural history studies are the crux of clinical trial design for the future. So they also have the added benefit of giving us information for people today like, what proportion of people with a particular muscular dystrophy go on to

developed heart disease, or what's the average rate of progression for breathing abnormalities? Things that are very helpful and inform your care today.

And I think the other thing that they do is they allow on the backend head-to-head comparisons about the way different clinics are approaching patients to see which ones work better, which ones lead to better outcomes. There are undoubtedly things that a person in one clinic is doing without realizing it, that is actually improving clinical care outcomes for a group of patients. And if we can see that in the data and pull that out, then we can quickly disseminate that idea to all of the FDA care centers. I mean, a good example from ALS is that we thought it was best to start non-invasive breathing machines when the breathing capacity had fallen by half. So we would watch very carefully to see when people got close to that 50% mark, we would suggest starting non-invasive ventilation at night. Now, there have been some good studies showing, hey, the clinics that started at 80% instead of 50% have better tolerability, people get used to it more easily.

They have a trend towards fewer pneumonias, their quality of life while using the machine is better. And so, hey, we need to get the word out that it's probably better if you can get the insurance company to cover it at 80% instead of 50%. And so practice changes like that can also come from these natural history studies. So that happens on the back end of coming to clinic MOVR Hub is collecting the data that we collect from every clinic visit, but just putting it to work in a way that we didn't used to be able to put it to work.

Mindy Henderson: Absolutely. And I think it's important to mention, correct me if I'm wrong, but there are privacy practices put into place, and if you choose to participate in the MOVR Hub or in an ALS Registry, there is no personally identifiable information connected to your data in those systems. Is that right?

Dr. Matthew Har...: Yes, that's absolutely the case. And that's not unique just to the MOVR Hub, but in research, we take confidentiality and participant privacy very seriously. I would say a third of our application to the ethics committees that approve our studies is devoted to the procedures that we're going to follow to keep people's identities protected, to make sure that confidentiality is assured. So yes, you're right, in the MOVR Hub and in all these registries, people can't be identified. We keep that information very closely guarded, and it's not available outside the center.

Mindy Henderson: Great. So I'm going to pivot now to a few patient care questions. Tell me, when thinking about, we've got this network of MDA care centers, why is it especially important now with maybe all of these changes in neuromuscular medicine and new treatments on the horizon? Why is it important for individuals to be seen at an MDA care center? What are the benefits of that?

Dr. Matthew Har...: Yeah, absolutely. So at that first MDA conference where I had the opportunity to present, I distinctly remember another presenter saying that only 1/3 of people with MDA diagnoses were being actively followed at an MDA care center. And that most of the other folks had basically were relying on their primary care doctor to get their durable medical equipment updated or to take care of things, but they'd essentially stopped coming into clinic because there didn't seem to be anything additional for them besides just to tune up of their equipment or refills of their medications. And that's now completely changed.

I think we've learned enough over the last 10 years in taking care of patients that the expertise that's available at an MDA care center will help anticipate what might be coming next and actually head off some of those complications and head off some of the problems that can arise. Secondly, by coming to an MDA care center, if it's a participant at the MOVR Hub, what we find on your clinic visit is going to help develop better care guidelines, develop those clinical trials like I was saying, and contribute to future care. But then lastly, we spend a lot of time in clinic connecting people to the research that matters the most for their disease, and making sure that when a treatment becomes available or a clinical trial becomes available, that people have the information and the access to getting into those clinical trials earlier, of course, because as you said, the earlier we treat these diseases, the better, the more likely we are to make a big difference.

Mindy Henderson: Absolutely. And it varies from care center to care center, but there's also sort of the multidiscipline practices that are available at care centers as well.

Dr. Matthew Har...: Yeah, absolutely. So it does differ. Some places have a social worker, some places don't, some places have respiratory therapy that is on site, and other places you have to get a referral. It does vary. Of course, one of the things the MDA is working on is trying to standardize that as much as possible to identify care gaps that might be filled where it's possible. But it's true, in the ideal world with infinite amounts of funding, we would make every MDA care center a one-stop shop where every body system that can be

involved in a neuromuscular disease can be cared for at the same visit to prevent those lengthy drives and the transportation challenges. So yeah, that's absolutely the case. And a really good reason to come to an MDA care center is to get the input. And I don't think it's just having easy access because somebody's there on site, so you don't have to set up another visit, it's also the collaboration between the multidisciplinary care providers.

So I can't tell you, I'm a pretty good doctor, I'm pretty thorough, but it's not uncommon for me to come out of a clinic room and for us to be talking about a specific patient in their challenges, and for the speech therapist to have detected something in their conversation with the patient that I overlooked or didn't key in on as a major problem. But they had shared that with the speech therapist, so I would be able to have a backstop and have somebody noticing something that I don't notice so that we can provide comprehensive care, I guess, is a good way to say it. So the collaboration amongst the providers allows us, I think, to provide better care overall for people with neuromuscular disease.

Mindy Henderson: So good. So if anyone is listening who is a patient or maybe a parent of someone who's going to be seen at a neurologist or a neurologist's office, or at a care center, what's the most important thing that a patient can do in preparation for that visit?

Dr. Matthew Har...: So this is maybe a little tongue-in-cheek, and I'm sure some of the busy doctors at your care centers are going to be upset at me for saying this. But I was going to say, in preparation, one of the things that you should do is make a list of really hard questions about your disease or your child's disease.

Mindy Henderson: Yes.

Dr. Matthew Har...: Almost, not really, but try to stump the dock, push the boundaries like, how much do we know about this gene? What are the gaps the things that we don't know? Do you know of places where I could help out, where my advocacy could really drive research dollars into disease X or Y? Kind of push your team to catch you up to speed on what's known about your particular disease or gene. I mean, that's not a prepare for clinic of the most out around care, but I think that that's something that people can do.

Mindy Henderson: I love it. And kind of piggybacking on what you said, I think just making lists in general because going to a neurologist's office or any medical appointment can be a little bit nerve-racking, and so I

think having a written list of the things that you would like to accomplish in that visit is helpful.

Dr. Matthew Har...: Yeah. And also in the days of electronic medical records with MyChart and ways of sending messages to your practice team, even sending that list of things you hope to accomplish in advance of the clinic visit means the team can be aware of it and be factoring that in to kind of know and help you remember the things that you'd intended to accomplish during the course of the visit.

Mindy Henderson: Nice. Now, this may or may not be a fair question for you because there are so many different conditions and variations of conditions and ages and all of the things. But, what is the most important thing or things that patients should do between appointments in order to maintain their overall health and wellness if they have a neuromuscular condition?

Dr. Matthew Har...: Yeah, you're right. So that is a really challenging question to answer given the variability amongst the different diseases. So instead, I think I'll key in on the wellness component of that question, because what you might do for your muscle strength or your heart or your lungs will differ between diseases. But what you can be doing for your mental health and for your overall wellness is extremely important. So two of my own children have genetic conditions that require a lot of visits. Neither of them are neuromuscular, but the idea is the same. We need to all take time when we're coping with challenges in our lives to set aside time to rest and reflect, and to take stock of where we are emotionally, to take time to grieve the things that are really frustrating about our diseases. I was just noticing the book on your shelf, *The Truth About Things that Suck*. As smiley as you can hear our voices being as we're having this conversation, these are still really challenging, frustrating diseases to encounter and to have.

And so, I think giving yourself the space and grace to take the time you need to be patient with yourself and with your kid or with the people around you because of these diseases and their challenges is really important. And then I think the other thing I'll say is that having a positive attitude in every condition it's been looked at, actually improves outcomes. When they've looked at it in cancers, people with the positive attitude do better than people with the exact same chemotherapy regimen. When they've looked at it in essentially every disease where it's been studied well, you see this effect. So maintaining a positive attitude. And frankly and honestly, from my own experience, it's impossible to maintain a positive attitude if you're not doing that first thing that I mentioned, which is

to take time to grieve the things that are really grievous about what's happening, to focus on being positive in the places that you can give time and space to yourself. That helps, at least within my own family, for us to maintain a positive attitude.

Mindy Henderson: Absolutely. And the book that you see behind me, I actually wrote that book, and one of the things that I talk about in that book is, to your point, so much about these conditions and any, frankly, challenges in our lives can be so devastating. But one thing that I kind of counsel people to do is to, as much as you can, focus on the limitations, to focus on the possibilities. Because even with diagnoses like these, there are still possibilities to be had, and I think it's important for that not to be shortchanged.

Dr. Matthew Har...: Yeah, absolutely. That's a really good way to put it.

Mindy Henderson: Yeah. I seriously could talk to you all day. I would love to put a coffee chat on our calendars once a week and just pick your brain on the regular, but I know that your time is limited. Do you have any final words of advice for our audience?

Dr. Matthew Har...: So final words of advice for people listening today revolves around the term of being proactive. I think with everything that comes at you, from my own family's experience, it's hard to create bandwidth to stay informed and to stay on top of things and to be proactive. But I think we're at this critical juncture in neuromuscular medicine where treatments are coming and they're around the corner. And so, being proactive about maintaining health today and staying informed so that you know what's coming is possible for the first time in neuromuscular disease ever.

So I think that's what I would encourage people to do, is to stay connected to your MDA care center, they can help with that education. Not everybody has the ability to go online and figure out what's up with research in their specific disease, but that's why organizations like the MDA, that's why publications like Quest Podcast like these exist, is to help people navigate that space.

Mindy Henderson: Perfect advice. That's so good. Dr. Harms, thank you so much for being here today. I know that our listeners are going to love this conversation and learn a lot from it, so thank you for giving us some of your time.

Dr. Matthew Har...: Absolutely. It's been a real pleasure.

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.