Dr. Ann Tilton: Thank you so much for allowing me to be here today. I'm really excited to talk about our topic. We're going to be talking about Duchenne muscular dystrophy and utilizing personalized treatments and addressing health disparities as we interweave through this disorder. So I'd like to talk about our learning objectives for today. So we're going to start by describing Duchenne muscular dystrophy and really emphasize the inter-professional care that's necessary to really provide these children and young adults optimal outcome. It's important to explain the different emerging therapies and how to incorporate these into these considerations of a personalized treatment plan. The prevalence of Duchenne muscular dystrophy in different ethnic and racial groups and address health disparities among individuals relative to their socioeconomic status, residential, geographic location, and the key access to the Duchenne muscular dystrophy centers. We are also going to recognize some of the environmental factors that impact this and their outcomes, but there's no better way to really approach these learning objectives than to understand the disorder itself. And one of my favorite ways of really looking at a disorder is to personalize it in the sense that we're going to be talking about a young man named John. This is a 10-year-old young man with progressive weakness that was noted when he was three years of age. And what we know about John as well is that he has difficulties climbing stairs and rising from the floor. He toe walks. He has pain in his calves and also some school difficulties, as you can imagine here. So as we look at this young man, we have to kind of assess what's going on. He's had a chronic course, he has the changes you can actually see here. He's standing on his toes.

And we'll see some more real characteristic findings of the disorder that we're going to be talking about. Well, you know, we're going to be talking about progressive dystrophies and specifically what we call a dystrophinopathy. And that's because the dystrophin can have more than one type, but the most prominent one is Duchenne muscular dystrophy. In terms of the specifics of it, it occurs in one in 3,300 live male at birth, and it's important to recognize that it's also a spontaneous mutation rate. And you're going to find that the reason that occurs is because this is such a huge gene, that there are a lot of sites where there can be abnormalities. Some of these sites are called

hotspots where more of the abnormalities occur. We also know that it's more prominent in white males, but what's important is that black and Hispanic males are often evaluated later and with that there's implications for implementation of therapy and probable outcome. And also personalized care is impacted because of the recognition and also the interventions that are required. So looking back at other types of dystrophinopathies, we're also going to address Becker's muscular dystrophy, because if you're working with children with Duchenne muscular dystrophy, then you're going to hear, is it Becker's or is it Duchenne's? And we'll talk about the discriminating points between the two, but very similar in a lot of the ways. So in terms of background, there are s some fascinating work that went on. It was well-recognized in the mid 1,800 that this disorder existed and a man named Gowers described it, and I'll show you some of his pictures. But it took to the 1980s to actually recognize where this gene occurs.

And if they map the gene, which you're looking at on your right is the X chromosome. And you can see that there are P areas and Q areas and specifically X, P21 is where the abnormality of Duchenne muscular dystrophy occurs. Finally by 1985, they could actually see it when they were looking at the chromosomes, which is pretty remarkable. Now, the thing that was recognized as well is that it is the largest gene identified in humans. It represents 1% of the entire X chromosome, which is remarkable. And that particular thing can actually be seen if we look at it by a microscope. So as we talk about it as well, what we also know is that the protein product of this gene is called dystrophin. Now Duchenne muscular dystrophy product, as I mentioned, dystrophin is part of a protein complex that I was hoping you could see here. And with that, what we recognize is that it's a very important component of it. And what it represents when we look at this is that it's the mechanical stabilization of the plasma membrane and this plasma membrane as well can have such things as scaffolding and structural changes in it. Now, if we look at this a little bit more closely and here- I think we're losing some of our pictures at this point, but what we do know is that it looks very different diagnostically what we can determine about the children. One thing is that's very important is that the CK is elevated. It can be dramatically elevated at 20 to 200 times normal. So

what we could say is if it's normally up to 200, then 20 times that will be 4,000. It may even be 40,000 in the children.

So with that, they have these dramatic abnormalities, often recognized they have blood work. This is maximum about three years of age because that's when they have the maximum amount of muscle. And this drops about 20% per year. Also because it has the damage of the muscle, other things such as elevated AST and ALT are there. And one of the diagnostics about this is to do an EMG and nerve conduction study. And the EMG is something in which we use a small needle and place it into the muscle, a pin, and listen to the muscle itself. And that muscle will be irritable and irritated. Other things about that is that we now can do things such as gene tests and in addition, muscle biopsies. If you look to- I'm hoping you can see the picture on the right. The one at the top is a normal muscle biopsy. The one on the bottom is one of someone who has Duchenne muscular dystrophy, and you can see that it's dramatically, dramatically different. In terms of other things such as the diagnostics and here we go, here's the dystrophin and if we look at the Western blot, this is important too. I mentioned that there is something called dystrophin. That is actually the gene product of this gene, and it could really be stained and then it could be recognized that this is what really separated out Duchenne muscular dystrophy. If you look at the slide in the upper right, you can see that this red outline circles around the muscle membrane and this muscle membrane, as I mentioned before, when we looked at the dystrophin that was circled there is the scaffolding that holds that muscle fiber together.

When it's missing, then the muscle itself tears, gets inflamed. So you're looking at someone who's a mosaic, which is probably a carrier mother, where there are spots that you don't see the circles and spots that you do. And that really represents the gene product because part of the fibers don't have the gene product and part of them do. The lower slide, however, you don't see any of these circles. This is an example of Duchenne muscular dystrophy. So they are not producing the dystrophin that they need. The technique is called a Western blot to quantitate it, but that is going

to be a discriminator between the milder forms, which is the Becker and the more severe form, which is the Duchenne. So then the thought is, well, if we could just get a bit of that dystrophin made or convert them to the milder form, then maybe the outcome will be different. And that will take us to the new novel therapies. So now let's get back and let's talk about our patient. If we talk about this, usually there's some problems below the age of two, but really very, very subtle. It looks as if gross motor delay. The mean age walking is about 18 months. We know that 14 months is about the time that the typical child may walk. So this is a little bit later. Now, clinically apparent at three to four years of age is a comment here. And what that tells us is that there are other characteristics that become apparent about that point in time.

Look at the young man on your right. And what you see is several things. If we could look at him in the grass a little better, he's probably standing on his toes. But there's one other thing that's quite obvious on him. You think, goodness, he really looks like he's got muscular calves. Well, he actually has proximal weakness. He does have calf hypertrophy, but it's not muscular. In fact, the muscle has been replaced by such things as fat and fibrous tissue. So it's called pseudohypertrophy, but it's a very classic finding. So you can be weak and yet it looks like you have lots of muscles. It also expands in the triceps and the arms, even the tongue can thicken. So what we know about dystrophin, this gene product or the lack thereof is that there are areas throughout the body that are really affected when one has Duchenne muscular dystrophy. I mentioned a historical perspective just a moment ago. And the picture in the upper part is Gowers' original drawing of someone with Duchenne muscular dystrophy in the 1,800. And what you can see is that they have this tilt of their pelvis, where they're leaning kind of forward. It accentuates that lordosis. And with that, they have the pelvic girdle weakness. So current picture, the one on the bottom is beautifully matched to what Gowers actually drew. So here's a young man with it, with a lot of girdle weakness. And a lot of times you'll see someone be able to walk still, but they have the weakness of maybe trying to climb stairs and other areas. So it's called a myopathic gait pattern. And some of you may be familiar with this particular term, but what happens is that the

pelvis, it can't be held straight. So they drop one side and they drop the other, often described as a waddling gait.

So if they come into my office, if this young man came in my office, I'd be very interested in watching him walk. I'd be very interested in seeing if he has the Trendelenburg looking at his back, having get up from the floor. And in fact, we frequently time lying down to standing as one of the monitors on how someone is doing. So this is going to become apparent around two or three. And in all honesty, they've lost a substantial amount of muscle by that point. So other things to talk about is that there's neck flexor weakness, and it often correlates with respiratory things. And I mentioned Gowers before, and his name was assigned to very important sign that we call Gowers' sign. So I'm going to take you through this. Here's a young man and he's sitting on the ground. We said, could you please stand up? So what does he do? He rotates forward so that he can utilize other muscles other than just standing straight up with his legs and his girdle. And then he climbs using his own body as struts and up he goes, and there, you can see him standing. So that is Gowers' maneuver. Now, what's also important if you're reading charts and saying this or even evaluating a patient, is that all that's Gowers is not Duchenne muscular dystrophy. And although the woman on the right could have Duchenne dystrophy because women are carriers and women can express it, what we see here is someone who has a different muscle disorder, but when she gets out of a chair, she's doing the same maneuver because she too is weak in her girdle muscles. So I mentioned about the neck flexors. I've also mentioned about Gowers' sign.

Another thing that's important is that there's a certain amount of intellectual disability associated with the diagnosis, as well as autism. Now, not all children with Duchenne dystrophy by any means have any intellectual disability. I have a young man right now who I'm taking care of, who's in college to become an electrical engineer. And I have great respect for that for sure, for the math and everything else. And yet I have other children who are in special education. And just as I mentioned, that that gene is very long and there are certain areas that are called hotspots that tend

to get the deletion. This also correlates with where the deletion is to a certain degree. So this hotspot around 40 to 50 because there're like 70 of these areas. Those are ones that really affect the muscle, the majority, and even heart, as we'll find out, some of the intellectual disability may even be expanded or in that of different areas. But what we do know is that there's a progressive course that is associated with that. So we've got to kind of work our way through what we need to watch for if you're monitoring these patients, or even if you're a case manager looking to see what the next step will be. So let's talk about the motor system and that's the one that everyone thinks of immediately. There is a honeymoon phase.

In other words, they seem to plateau between the ages of three and six. I mentioned that they begin to be identified around that age, maybe because they had blood drawn for another reason, and they get concerned about some of the lab being abnormal. And then they're very concerned that it's dramatically abnormal when they look at that CK. But between three and six, they seem to be fairly stable. And yet it still represents they've lost about half of their muscle mass, which points to the fact that we're going to treat. We definitely want to treat early if we possibly can. But that's sort of goes along and things seem to be doing pretty well and they're walking. Between six and 13, just an average, then there's a linear loss of muscle mass, a linear loss of abilities. During this time they're also growing, which impacts just the different ways that the vectors of where they're standing and how the lengths are, as we all know, as you get taller and maybe with weight gain, it becomes more difficult. And simultaneously they're losing muscle mass. It levels again around 14 to 15, but by this point, people really are quite weak. So what is the predictor of ambulation? If someone is in my office or someone's asking you, how do you know that there's going to be, you know, someone who's going to walk or not walk and when are they going to lose it? Well, we use tests just mentioned getting people up from the floor.

If it takes greater than 12 seconds to walk 30 feet, which could be marked on a floor, then the predictor is that they will probably be losing ambulation within the next year. And that just is

representing the fact that they are, at that point, probably getting weaker and slower and balance is an issue. So what about wheelchair use? That's a very, very big piece of durable equipment that's needed. Often the schools become very concerned because they're worried that the child will fall in school. And also just even getting between places. I mean, getting there is important, missing lunch is terrible and getting to your classroom is critical. So that becomes very important. And what we know is that the child who is untreated is probably somewhere between 7 and 13 is going to begin to lose the ability to walk independently and also to where just even distances are overwhelming. So the average is at about 10 years of age, if they're untreated. What we also know is if they go to over 14 years of age untreated, then that's probably that milder Becker's muscular dystrophy form. I put or LGMB- D rather, which is limb girdle muscular dystrophy. We're not really talking about. But what it really says is this isn't consistent with the diagnosis I'm thinking of. Could it possibly be one of the other forms of muscular dystrophy?

And I had shown a picture earlier with the scaffolding and all of that. And if you were able to see it, what you realize is that there are all different sorts of disorders that can be associated with the muscle membrane. And this is one of them, the one that performs that does the scaffolding is the Duchenne's or the Becker's. They look very similar on biopsy. And here's a picture of a young man who would have the same biopsy and yet is still walking. If you look at him, you can see his calves are large. You also can tell he's quite a bit older and he doesn't have that striking, striking findings that we've already been talking about. So what else are significant and concerning progressive parts? I want to talk a moment about scoliosis because it's quite serious. And it's something we monitor consistently. We have our muscular dystrophy association clinics or our neuromuscular clinic. At that point, we have orthopedics, we have neurology, we have pulmonary, we may have physical medicine. We have PTs, everyone looking, and then we can send them off to get bracing or whatever. They get an x-ray not only for their chest, but for their spine almost every time they come in. And there's some protocols and guidelines on this, but clearly every six months and some people much more often. So as we talk about this, and here's a picture of an

older historical picture, as you're looking at it of someone who has what they call calipers, these braces. So they were doing their best to keep them standing.

But in truth, they're just basically resting on those braces. So the scoliosis, its prevalence can be up to a hundred percent of the patients. So you should expect it. It correlates with age just as the progressive nature of the disorder does. And by 15 years of age, 50% are going to have substantial scoliosis. And if you're familiar with how we measure this, it's how many degrees of curvature there is. If it's 11 degrees, that's a progression, but 42 degrees, you can imagine you could suddenly become 90 degree curved. And that is a very serious and difficult one, very difficult to brace after about 35 degrees total. So it's not something we can brace very easily and usually don't in all honesty. So the progression goes on a yearly basis, but we're monitoring that very closely hoping to keep them stable. And one thing that was thought was and it is true we want to keep people walking as long as we possibly can, but the thought was, oh, once you're in a wheelchair, you're going to get terrible scoliosis. And what they found in the science was no, it's not that being in the wheelchair itself is causing the scoliosis. The problem is that you are in the wheelchair because you're weak and because of the problem. Now, I would like to talk a little bit more about the main distinction between Duchenne muscular dystrophy and Becker's muscular dystrophy. And that is that there's wheelchair dependency. And if you are less than 12, at that point, as I mentioned, then you're going to have the probable Duchenne's. If you're over 16 years of age, then you probably had the Becker's form that we were able to see. And between those two, that is the usual occurrence. So let's talk now again about this progressive disorder, but a little bit different area.

I want to talk about the cardiac symptoms and in all honesty, the muscle becomes weaker, but cardiac, the heart being a muscle is often one of the most severe problems and often leads to the demise as does the pulmonary, but the cardiac problems are significant. And so these patients do need frequent monitoring by our cardiologists. Now 90% of patients will have an abnormal EKG and they'll develop a cardiomyopathy, one third by 14 years of age and it is assumed that all of

them by 18 years of age. The echo shows the left ventricle is the most prominent area of abnormalities and the milder forms. And I do have some patients where their muscle disease was not much of an issue at all, but they went for heart transplant because that's the muscle that expressed the abnormalities from the Duchenne muscular dystrophy or in that case, Becker's probably. One thing I didn't include here that I really, really want to emphasize however, and that is that the carriers, the mothers, and it must be seen by cardiologists as well. We have lost patient's parents, mother because she has the cardiomyopathy and was unaware of it. So we are very conscientious about sending every one of these young men's mothers to go to get to a cardiologist. I mentioned it can be spontaneous and she may not have any abnormalities, but you can't check it just by blood.

You really have to get these people checked because they can have the arrhythmias and progressive left ventricular failure. And then you've lost a family member who is probably the primary caregiver, which impacts their long-term care as well. So and when they go to the cardiologist, the thing that they're doing now is starting medicines earlier. The ACE inhibitors are specifically that. And so some of the heart management is looking better. And we'll talk more about the heart management, where some of the therapies we're using separate from the heart medications, things such as steroids, which is going to be very important and was a major breakthrough. So what about orthopedics? They have been a critical part. I mentioned they're incredibly important part of our team. They help us with emphasizing stretching. We use ankle foot orthosis, which is AFO's resting night splints because as you can see, standing on his toes again, that's one of the places that gets contracture, particularly when they're sleeping. Their feet get tighter and then shoe wears tougher and ambulation becomes even tougher. The way that the muscles get contractures, not just contract, but get contractures, it tends to make them stand on their toes just because of how their back is lordotic and it pushes them forward. So they do have to stay on their toes for balance as well. So less of getting the heel cords released now at this point

in time. What we're going to talk about as well is the input of exercise, which makes a difference in patients, which we're happy to say.

And in addition, that scoliosis that I emphasized a moment ago is really closely monitored by orthopedics. And they're the ones who will intervene with surgery when it is necessary. And hopefully, they'll get skeletally mature, but most of the children, if they really develop scoliosis, need surgery ultimately. The other major issue is respiratory and questions I ask in the room to give me more hints. When you're talking about the heart, you want to know about fatigue, you want to know about fast heart rate. You want to know if they're breathing fast, but respiratory, particularly, I always ask them, how do you sleep at night? Do you have a lot of nightmares? It seems a little far-fetched, but what's going on is if they are retaining CO2 or they're getting apneic, they're waking up multiple times a night and even having more vivid nightmares and dreams. So that's a way- so if I have a patient who wasn't doing that, and now they're not sleeping well and they're waking up multiple times, it raises a red flag. Same with headaches. Same with daytime sleepiness. If these individuals are really waking up tired, then you go, I bet they're really not sleeping well. And we need to see if they need nighttime ventilation, non-invasive and just to be sure they're safe because if you're not sleeping and you're tired, then it's going to impact the muscle directly too in the sense that your strength is going to be lower.

So pulmonary colleagues have well-recognized this, have guidelines that they really implement for our patients. And forced vital capacity are done once or twice a year. So one takes a deep breath and breathe out as hard as they can. So in that test, you're checking what's the restrictive nature of the lungs, how much air are they moving? And that gives some real important information as to whether intervention is needed. Noninvasive measures are important. In the upper right, you see a young man who has pressure placed on his nose and it's driving air in to stimulate him to breathe and to force a little bit of oxygen, but it's not really a ventilator. You can also have negative pressure kind of the old iron long situation. You can also have positive pressure and this young man on the

right, he may have a trach and have a ventilator with him that they've elected to do positive pressure. Other things that can be done that are important is something called a vest. So as the cough gets weaker, they may be able to just wear this vest and have some respiratory improvement because of that. That vest vibrates and utilizes just that motion, just like CPT to mobilize the fluids and help. GI, it's smooth muscle, it's also affected. And one of the things we have to deal with is the intestinal lack of mobility, even swallowing sometimes. So we have to pay attention to constipation. We have to pay attention to how are they eating? And what's interesting is that early on it's often obesity that's a problem, probably compounded by steroids, but the obesity is a major issue. And the heavier you are, the more difficult for you to move.

But in addition, as someone becomes older, then their caregivers are going to be faced with transfer. So equipment becomes very important, Hoyer lifts and other things. And that's a major issue. And you can see this young man on your right. It seems like the children are either and the young adults either obese or significantly malnourished, maybe because the intestinal hyper motility, maybe because of some depression and other things that occur. With that, we know that there's osteoporosis. What you do know as well is that we pound on our bones by walking. We pound on our bones everyday by lifting weights. And that's how you get the calcium back in your bones as you get older, particularly. And so people take calcium and vitamin D supplements just for their general health. This group is particularly important and what's interesting is they become osteoporotic or they lose some of the portions of their bone or the strength of their bones, even while they're still walking. So you have to pay attention early. We do put them on calcium and vitamin D supplements. You need about a 1,000 units or milligrams of these a day. So we'll often give a 1,000 of calcium and 2,000 of vitamin D just to see if we can try to really get some of that calcium, not mobilized, but put back in the bones. What's interesting too is right now, we've been so conscientious- we in the royal sense about sunscreens that most people I run into are vitamin D deficient and even in Hawaii, believe it or not.

So we do have to be conscious of that, and vitamin D is an important part of this supplement. If you have broken bones, then IV forms of medications that will put that back into your bones. It's also here, the bisphosphonates and the DEXA scan is a scan that looks to see if you have osteoporosis or other abnormalities of your bone that may need further intervention. One other thing to remember is that these patients can have an anesthesia reaction. And I can tell you I've had several patients where I met the child in the recovery room because they had an anesthesia reaction for getting their ears done or their tonsils removed. And before they could even get them under anesthesia, they had a very severe reaction to the anesthesia of certain types. And those certain types are ones that are inhaled or we call depolarizing, but they're an inhaled ones. So now anesthesia as an entire specialty now is much more sensitive to that. And if any of my patients have any sign of a muscle disorder, we make sure that anesthesia knows it and the family tells them because it can be avoided. You can have very successful anesthesia, very successful surgery, and yet, you know, avoid all of these consequences, if you know that. Now you say, well, that poor person who had the tonsils and the PE tubes, they didn't know at that point, but that's where anesthesia has made advances and can really avoid that much more successfully, particularly in a family history. But anesthesia is something to always keep in mind.

Now, I want to emphasize one other thing here. If there was ever complex care needs, this would be a group, as you can tell, that would need it. There are multiple systems involved. There's muscle system, cardiac system, pulmonary systems, GI systems. We in addition have potentially cognitive systems. We have psychological things and there are incredible social impacts of this. So complex care and multidisciplinary care is important. So what are the social impacts? Well, I mentioned cognitive deficits now a couple of times, but there's also the psychosocial factors such as anxiety or depression. Now this could be obviously very related to someone who isn't able to keep up with their peers, who isn't able to do things other ones can do and have fatigue and these physical limitations. We can't forget that there are environmental barriers as well, because someone who has weakness and their walking will be slower. Someone who is on a wheelchair

will meet those environmental barriers as well. And just the difficulty of entering stores and entering other places. If we're what they call able-bodied, able to just jump up the stairs, that's one thing, but that can be a barrier and an obstacle to a point where someone can't join you if they're in a wheelchair. So we have to be cognizant of that as well. And the disparities, this can be based on ethnicity, but also socioeconomic status.

The care is predominantly in the muscular dystrophy association centers, the MDA, which has provided a lot of money in early recognition of the needs of this group of people. So that center has an access issue as well. And what kind of access I'm talking about now is not the ramp, but the access is in fact, the access to care, because if you're living somewhere that's outside in the rural area, or if you're in a socioeconomic situation where you can't ride and get some help to get somewhere, that also is a limitation. So the multidisciplinary approach is very important. And what you can see is that their goals that's obviously strengthened functioned at all times, prevention and treatment of spinal deformities, addressing the respiratory and cardiac needs, clearly outpatient and home-based management, very, very important, and what we can do to help the parents and caregivers of these children so that they can have a good home-based management that allows for the caregivers also to have some relative respite and also that they can have outpatient care and I mean, our child's job is to go to school and to get them there and to have optimal experience outside the hospital.

Now, speaking of that, improved quality of life and reduced emergency care and hospitalizations is a major goal. And what we know about low socioeconomic group is that there's less outpatient visits and more emergency care and hospitalizations. So the more we can do a multidisciplinary approach, the more that we can recognize the complex care, the more we will be able to reduce emergency care and hospitalizations, which is better for all, obviously. Certainly, don't want to be in an emergency room right now where you could catch other things because you've run out of medicine or because you've had other problems. So now I'd like to talk a little bit about therapeutics

and some of these are just the basics, and then we're going to get into some very interesting things. So with weakness, is there a role for exercise? And the answer is yes, not maximal, not your trainer like a football trainer. Instead, what we see is that it's actually submaximal, low impact aerobic exercise. So you want someone interestingly not to go downstairs, climbing stairs, maybe, but you don't want to say, give me five more like you would some sort of a football player. Instead, it's all about aerobics, endurance and I always tell, I have the 20-minute rule. If it takes more than 20 minutes to get over your exhaustion from something, if you cramp, if you have a red mark that doesn't go away in 20 minutes, if it takes you more than 20 minutes [inaudible], all of those things tell me that you've overdone it or you need more support. So not to cramping or exhaustion, but what's the outcome? 20% increase in strength.

That's pretty good therapeutic, endurance improves, less fatigue and overall wellbeing. So something as simple as advocating for exercise can be a big, big therapeutic in these children and young adults. So the main stay, the most important thing that's often used now is glucocorticoids. So that's going to be deflazacort and prednisone here in a moment. So we used to say, well, how old should they be? Well, there's that plateau phase. In fact, some children younger than four have problems, but we tend to start around four years of age and older. I've had to start earlier, two and three years of age because there were siblings and the younger child was worse than the older child in terms of time to walking and getting up from the floor. So we elected to begin steroids earlier than the four. So this is a guideline, but not absolute. What we know about prednisone, we pretty much know about deflazacort, although there's been some recent data that came out that said deflazacort may have some advantages. But the data I'm showing you here is based on prednisone. The strength increases 11% and was maintained in the study. So that's good. They importantly ambulated 3.3 years longer. And if that correlates with scoliosis, you can see why the risk now is 20% versus 92, major difference in that regard. Forced vital capacity of their respiratory, findings improved and we've been waiting for this. And at least there's some data that it reduces heart failure. So it affects the muscle of the heart as well.

So prednisone and deflazacort are very important. They're not simple. If you've ever been around steroids or someone who had them or taking them yourself, you can imagine the appetites go up a lot, mood is affected. You have to get cataracts checked. It affects the bone just like we were talking about osteoporosis. So it is not a perfect medication, but it is clearly advantageous over no medication. So I've talked about exercise, I've touched on steroids and we can talk some more about, but I want to take you to some other areas, novel therapies. It has been- research has been dedicated to this topic for quite a while. And I'm just listing the ones that are not highlighted just to give you an idea of some of the things that have been done. We know there's an immune response. So suppressants were tried, didn't work. Myoblasts transfers, where they took normal muscles transported it into others to try to get that dystrophin back in there. Other ways of doing things, even viral vectors, where they did gene therapy, you hear about gene therapy that you can give the gene that can deliver the missing exon we'll talk about. And it looks as if at least in some of the preliminaries, there's some optimism and some others, it looks like the body has rejected it and there wasn't much effect. So stay tuned clearly on gene therapy that would get back to the origin of the problem.

So I want to talk about exon skipping, which is a fascinating topic. So as we talk about these, they're designed to increase the production of dystrophin. Dystrophin is that product of that gene and we want dystrophin. It's making that circle on those muscle fibers you saw. It is the scaffolding that keeps the muscle from tearing. So what it did and what they did in the studies was to find a way to increase the production of the dystrophin. These include several medications. You can see four of them here, and they are directly affecting exon 51, 53 and 45. You can see the percentages of the patients who have Duchenne's dystrophy next to that. So 13%, eight, eight, and eight. So it is trying to target some of the more common exon things, that hotspot I was talking about. And so what they're going to do is try to skip over that genetic code where the error is, and it allows production of a shorter, but a functional protein. Before I show you the picture of this, I want to

show you one other thing that's a bit startling. So here are the four medications plus deflazacort, that steroid, I mentioned. Mutation 51, 53 and 45, all age groups on this skip, the first four, all delivered weekly and this is the price tag per year, somewhere between $300,000 and $750,000 a year. Now, if it makes the difference of living and not, that's a different issue. That is all being looked at currently and there was clearly in the studies optimism that it made a difference, although that's still looking at long-term.

The deflazacort is started around two years of age, it's a daily medication. Steroids can be daily or just weekend, but deflazacort is about $82,000 a year. So these are serious medications and some serious price tags, as well as all these new medications are being developed. So I want to talk a little bit about an example. This is skip exon Exondys 51, and this is borrowed from one of the primers. And what you see at the top is pre-mRNA. So what that top recipe does is develop the protein. It develops the dystrophin that we want, but what you can see is there's exon-intron, exon-intron and the exons are the numbers I'm talking about. Unfortunately, the one that's green is a mutation and because it has an abnormality, when it is red and made into a protein, the protein doesn't work. That's your lower left. So it's non-functional. You can make it, but it's not going to help. It's not going to put up the scaffolding and you're going to have muscular dystrophy. So what they did is just absolutely remarkable the way scientists going is they went in and said, let's use exondys 51. We're now going to skip that abnormal mutated one. We're going to connect now orange to yellow, and now we have a more functional protein. Can we make this child not a Duchenne, but a Becker's by having more functional protein, although it's not completely normal? That means they'll be walking till 19.

That means they'll be living longer. Their hearts will be better. So you can give this with steroids as well. So you're trying to make the more functional protein. I hope that sort of make sense of this, and you can imagine the development of what that takes. And so when patients come in and we do the gene test and we know what exon is missing, then we know whether or not they can

benefit from this sort of a jump strategy, the exon skipping to make a more functional protein and the percentages you've seen. There's one other one that is in Europe, not in the United States called [inaudible] and up to 15 patients have a sudden stop of one of these codes. And because of that, they make an abnormal protein. And this actually, again at that code on 51, 53, they bypass that mutation and are able to make a functional protein by different mechanism. But indeed it converted again to maybe a Becker's at best. So I'm going to get an opportunity to stop here and be able to answer some questions, but the conclusions and the thing I want you to really remember is that, although this is very complicated, there's so many more possibilities out there. There's so much more optimism. And I can tell you compared to talking to parents 20 years ago, talking to them now allows me to say there are possibilities and hopes and greater optimism. And it's a very, very nice place to be to say, there's a lot of interest in research. So hopefully, we can make all these children better, and that's the overview. So I'm going to turn to some questions and see if I can answer those for you.

Rebecca Gleason: Thank you, Dr. Tilton for an excellent presentation. I just wanted to give a reminder to the audience that questions may be asked via the instant message box that's located on the bottom left-hand side of your webcast player. Thank you.

Dr. Tilton: Okay. I'm going to open with one. I think it may be a little difficult to answer, of course. One of the people ask, I have an infant member with the diagnosis of muscular dystrophy, but when the genetic testing was performed, they said it does not differentiate the type of muscular dystrophy. I think probably we'd need to really look at this. It is true that there are variations of unknown significance that probably have not been identified in multiple patients and therefore they can't say that. When we send off the gene testing, it tests for like 160 different genes. It's absolutely remarkable. And they're usually able to identify specifically which one it is. And if they're really influenced, they may need to look at this again. They may need to test the parents and find out if the parents have the same variations of unknown significance, and if they're not affected and the

child has it and is affected, then they may be able to say, this is a specific type. The other aspect of this is, can it be false positive because mother is on anti-epileptic medications? This should not affect the gene test. It is true that epileptic medications do affect the child. They just have more difficulties, but it should not affect the genetic testing. I would think that that just needs to be looked at it again.

Another question is, how do we diagnose Duchenne muscular dystrophy? Can it be seen in newborn or is there a particular age? One of the things is usually the infants look perfectly fine and that helps us differentiate the type of disorder. If they're born and they are floppy from the very beginning, that is not going to be Duchenne or some other form. It could be one of the other forms of muscular dystrophy, one known as- several known as congenital, some known as other things. But if it then follows the course, sort of progressive, a little bit more chronic, a bit of delay of motor skills early on, then by the time they're three or so, it's interesting that recently in clinic, I've seen two children that were probably seven to eight years of age, who hadn't been diagnosed yet. That's really unusual, but it's hard to see then a particular age of probably around three. Now, another important question. What is the typical lifespan for a person with Duchenne muscular dystrophy? And now I get to say it depends on whether or not they're treated because the usual thing I had to say 10, 15 years ago was late teens. By the time they're late teens, the cardiomyopathy usually was the limiting factor, also respiratory, but with interventions and even earlier intervention to keep their lungs healthy, they are living longer, but the cardiac is often a major limitation.

So in the children who get steroids, we now have patients into their twenties and thirties. Gene therapy obviously would reverse the whole thing. We don't have enough data yet on the skip exon, but they're on steroids as well. So now it's twenties, maybe even into their thirties. One thing that's important if you're on steroids and you say, okay, I'm done with them now, then it's not- you know, you may lose some of the grounds you have, that was at least part of the thoughts. So it really is an extended period of time to be on steroids. Sometimes later in life, people will reduce them or

come off. We'll also reduce them if there's some of the side effects. Oh, one thing that is important and someone asked this question, I really didn't delve in it because of time. I mentioned that Duchenne muscular dystrophy is carried on the X chromosome and therefore is much more prevalent in men or boys than girls. It is possible that a female, a girl can also express it. And this has to do with the males having only 1X, therefore they fully express the disorder and females have two Xs. And it may be that one of their Xs is the abnormal X. And that's how they pass it onto their own children.

Since we only use 1X ourselves as females, then if they happen to suppress all of the normals and are just X abnormal, then they will look like a Duchenne. That's very rare, but we see it. And in between is the carrier state. So the ratio of expressing in males is much, much higher. In females if they do have enough of the abnormal Xs, then it's much milder than it is in the male, but I've had a patient who was a female, who was in a wheelchair by the age of 10. And we wanted to put her on steroids and everything else and treat her just like a male. And her mother was a carrier with no symptoms. So it is complicated. And again, sometimes this can be spontaneous, but it is much more likely in the males because they only have 1X and it's abnormal. One question as well, was, is there a specific genetic panel to identify the mutation causing Duchenne muscular dystrophy? And the answer is definitively yes. And you can do it at any point in someone's life because what they can do is a cheek swab. We don't have to do those muscle biopsies anymore. You can do spit. Hard to imagine, you can just put saliva in this capsule and send it back out.

There are some panels that are being done free by some of the companies. I don't know if I can share those or not. Some of the major companies also, you know, will run that for you because they can run the panel. And what's important when it comes back, in addition to helping us identify, number one, they'll say it's Duchenne muscular dystrophy with an abnormality of exon 51. That point, you know that they would be eligible for one of the skip exon medications. And that opens up a whole new panel. In addition, if it's positive, then steroids to all the detail that that I mentioned.

They give us the information and some of the companies will in fact say that we have genetic counselors available just to answer questions specifically for the physicians who are sending out the panels. We utilize our genetic counselors, critically important people that really are so well-versed in all of this and are able to really explain it. Another wonderful- some of the other wonderful resources is that you will be able to see different- such things as up-to-date and such physician information, but also information for families that really brings forth what is muscle disease, why is it this, what does it mean in a very sort of appropriate level and then the physicians can take it to the next level and explain it, because it's incumbent upon the person who ordered the test to really explain it more to the family.

One other important question is, is the genetic panel always covered by insurance? That's a problem and another health inequity that really should be emphasized. It depends, is the answer. Right now, we have the families talk directly to the company because of some of the programs where some of the companies that are looking for patients with specific exon abnormalities or other types of muscle diseases are supplementing the company so that they can get the tests for free. So we can do that. And they also will work with company- excuse me, work with families to see if they can't get a reduced price that's at least accessible. It is true that genetic panels are often called under question by insurance, which is a significant problem. And you can understand where a company wouldn't want to say, okay, let's start a million-dollar therapy, but do we want to spend 5,000 unless there's a real evidence that this might be an abnormality, but still it becomes a problem for someone who is not a strong advocate even for themselves, or don't have access to an MDA clinic in this specific case, because as a provider, I become a very strong advocate and can pitch fit or jump up and down, whatever to say, please, this patient needs this test in order for us to appropriately treat. Where if someone doesn't have access to that or in a rural place, they aren't going to have that type of advocacy and not because someone's negligent, it's just that they may not have the background to say this is important and a compelling argument.

So it is important to recognize that anything that's clearly like even over a certain amount insurance companies scrutinize it, and it's a much more difficult thing to get prior approvals. One of the other questions that came up has to do with behavioral health diagnosis and how many people with Duchenne muscular dystrophy also have that. And I think that that's a broad question because some have the cognitive issues. Some have autism, which is a behavioral health problem. But it is true that depression and sort of the overall accompaniments of that, with fatigue and everything are fairly prominent in this group. I don't have an exact number, but it is very high and should always be asked about, because referrals are important for that as well and we know that's hard to come by, but also just recognizing we understand that this is a very difficult thing. It's a chronic illness and we know from numbers that chronic illnesses frequently have behavioral health issues, which you know, is something that is important for life and independence and best outcomes.

I think we only have time for one more question, if there are any out there. This has been incredibly enjoyable with very good questions, and I hope that it does bring a lot of information. One question did come up about sexuality and childbearing potential. It is true that there are some who have significant muscle diseases that do go on to have children. It also needs a lot of genetic counseling because if a male is affected, his X is affected. So if he has a female child, not a male, it can't be father to son, but he, in this case, has a female child. It is going to be- that child is going to be a carrier. And if mother carries it, then that would be combined. But clearly the only X father has is that, but they do have sexuality. They do have childbearing potential. And it's a very important question as they enter into adolescence, because it's a lot of things we don't talk about but is part of normal development and part of growth and part of young adulthood. So that's another reason that counseling and everything else is incredibly important. Often we involve urologists. We involve other people as well. But that was a very lifeline question. So with that, I want to thank you for your attention and some of you giving up your lunch hour, and I hope this has really addressed a lot of questions that you might've had, as you entered into this. So thank you again, and I wish you well.