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Spinal Muscular Atrophy: Optimizing the Management of Adults in the Era of Disease-Modifying Therapies

Announcer:
Welcome to CME on ReachMD. This activity titled, "Spinal Muscular Atrophy: Optimizing the Management of Adults in the Era of Disease-Modifying Therapies" is provided by Clinical Care Options, LLC in partnership with Cure SMA, and is supported by educational grants from Biogen and Genentech, a member of the Roche group.

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Dr. Shieh:
I'd like to welcome you all to today's continuing medical education program, Spinal Muscular Atrophy: Optimizing the Management of Adults in the Era of Disease-Modifying Therapies. I'd like to thank the Maine Neurological Society for hosting this important program. This program is provided by Clinical Care Options LLC in partnership with Cure SMA, and supported by educational grants from Biogen and Genentech, member of the Roche group.

I'll be your speaker today. My name is Perry Shieh and I'm a Neurologist Clinician primarily at the University of California, Los Angeles, and Professor of Neurology and Pediatrics. This program was actually developed with largely input from me, I had actually developed a lot of the slides, and so, hopefully I'll be able to answer any questions that you may have on this content of this program.

Here are my financial 352isclosures.

OK. Well, very good. So, at this point, these are the learning objectives that we have for this program; A, to discuss the unique clinical issues and psychosocial needs faced by adults with spinal muscular atrophy. So, we are focusing on adults with SMA. Assess the latest safety and efficacy data for available and emerging disease-modifying therapies for SMA in adults. Third one is, to integrate available disease-modifying therapies for SMA into individualized evidence-based treatment plans. And the fourth one is, apply effective communication strategies to engage patients in shared decision-making and reach management decisions that meet their individual needs.

Just a little introduction is a motor neuron disease. It's a progressive genetic disease that results in the motor neuron degeneration that we see in these patients. So, over here on the right is a cartoon that illustrates the motor neuron, which is colored here in blue, and it is an autosomal recessive disease. And so, the SMN1 gene is most of the time deleted, or there are other types of mutations that can occur. But basically, there is a loss of function of both copies of the SMN1 gene. And so, this results in a relative deficiency of the SMN protein. Patients are not making enough of the SMN protein, and the SMN protein plays an important role in the survival of these motor neurons. And in fact, SMN stands for survival of motor neuron.

We have traditionally classified SMA into clinical types based on the severity of these patients, and of course this is now evolving because, really these were defined based on patients that were not treated with disease-modifying therapies because before 2016 there were no disease-modifying therapies that were approved for use. So, the most common types that you may have heard of are Type 1,

Type 2 and Type 3. There are also some that are on the edges of these severities, the most severe ones being Type 0, which are exceedingly rare, and these are babies that are born hypotonic. We typically do not see that. Most of the time the severe types of SMA are Type 1. And they may look relatively normal at birth, but then they never achieve the ability to sit, so they have manifest hypertonia and weakness within the first few months of life.

Type 2 patients are defined as patients who did sit but never walked. And so, these are patients which would have manifested clinical signs of disease usually after 6 months of age, but before 2 years of age or 1 ½ years of age. Type 3 patients do achieve the ability to sit and walk, although they may lose the ability to walk as time goes on. And at the mildest end of the spectrum are Type 4 patients. These are patients who appear relatively normal until adulthood, when they start to develop progressive weakness.

Today, we're going to be focusing on adults, and as you might already realize, Type 0 and Type 1 patients typically do not have the longevity to be able to live to adult, and hopefully that will change as disease-modifying therapies become more widely used and as these patients age. But at this point patients that you're seeing in the adult population with SMA are Type 2 and Type 3, as well as Type 4 patients.

So, this is just a little bit about the genetics. This gene SMN is located on chromosome 5Q, so that's the long arm of chromosome 5. And a healthy person may have one or two copies of SMN1. Now, a perfectly normal non carrier has both copies. If you are a carrier then you would have one copy, whereas patients who are affected by SMA, because this is a recessive disease, they have both copies of SMN1 mutated or deleted.

What you can see here is that SMN1 is the gene that's primarily responsible for this disease. SMN 2 is over here on the left, and it's a gene that's a little bit different from SMN1. It's really only different in a couple of different nucleotides. And in fact, SMN2 is able to make a functioning SMN protein, but it does so at a much lower efficiency, and we'll talk a little bit more about that shortly. So, as a result, patients with SMA do make SMN protein, they just make less of it, and the amount of SMN protein they make is largely dependent on how many copies of SMN2 that these patients have.

So, this gives you a little bit more detail of why SMN1 and SMN2 behave the way they do. This is the genomic structure, so this is what the gene looks like for SMN1 and SMN2. So, these are the way we number or label their exons. The exons are essentially the coding regions of this gene. And as I stated earlier, SMN1 and SMN2 are nearly identical, there are only a few nucleotides which are different, and one of the most important places where it's different is highlighted here in red. And that actually does not change the protein sequence of SMN2, but it does change something that we call splicing. And so, this is what this slide here is showing is that SMN1, when it goes through splicing, so that's after the DNA is copied into RNA, so that's transcription, it undergoes splicing where the introns are removed and all we have are exons. And so, these are exotic sequences in the messenger RNA, and this contains the code that encodes the SMN protein.

SMN2 is a little bit different because this one nucleotide change here, this T, actually changes the way exon 7 behaves. It encourages exon 7 to be excluded, so it's sliced out. That only happens in about 90% of transcripts, and so that's what this slide here is showing is that the messenger RNA that results from SMN2 often, in fact, most of the time, has exon 7 excluded. And this results in non-functional protein within a truncated protein. It does have some alternative splicing, as we call it, so it's a little bit leaky. And it is possible that SMN2 would result in a full-length messenger RNA and that would actually result in functional protein.

It's important to point out that patients or people who do not have SMA don't really care about their SMN2 gene. The patients with SMA, they're missing their SMN1 gene, or it's significantly mutated, and as a result, the only functional SMN protein that they're going to make is actually going to be made from the SMN2 gene. And so, that's why I say that the SMN2 gene is a weaker, or it's a gene that is able to produce SMN1 at a much lower efficiency. So, a person with SMA is missing their SMN 1 gene, but they may have multiple copies of SMN2. If they have, let's say, 3 copies, they might be a little bit milder than somebody who has only two copies, or somebody who only has one copy. So, these patients all have SMA, but they probably have different severities. And through various different studies, we can potentially predict, and you could say it's not perfectly predictive, but you can predict with some degree of probability what the severity of the patient might be. So, if you have two copies of SMN2, these patients are typically Type 1, the most severe types.

If a patient has three copies, they generally are not Type 1, they're usually Type 2, and some of these patients might even be walkers-Type 3.

If a patient has 4 copies, they're very, or they're almost certainly going to be a walker-Type 3 patient. There are actually rare cases of also 5 copies and 6 copies, but they're exceedingly rare. But those patients most certainly would be walkers.

So, here is a diagnostic algorithm. Basically, if there is a patient who is suspected to have SMA based on the fact that they have progressive weakness and neurogenic signs, such as fasciculations, you might even have a patient who's undergone an EMG nerve

conduction study which demonstrates findings consistent with premotor neuropathy. And these patients can undergo genetic testing, molecular diagnosis. And so, that diagnostic test is focusing on the SMN1 gene. And so, the SMN1 gene can be tested to see if it is present or if it's deleted, and if it's a homozygous deletion, meaning the SMN1 gene is not present at all, and this is most of the cases of SMA, then the diagnosis of SMA is confirmed.

However, it's still possible to have SMA even if both copies of the SMN1 gene are not deleted. They could, for instance, have one copy of SMN1 that's present, and that one copy could have a mutation, let's say, point mutation, or some other kind of mutation. And that could also result in SMA, so it's important to perform sequencing of the SMN1 gene. And if there is a mutation that's found in that SMM1 gene, then the SMA diagnosis can be confirmed. If the sequencing does not result in a mutation, then SMA cannot be confirmed and you may consider other diagnoses, other types of SMA for instance, or even look for other diseases like muscular dystrophy or other muscle disease.

So, we most certainly are moving towards molecular diagnosis and it's also helpful to test for carrier status, so you can do carrier testing using a number of different methods, including what they're showing here, quantitative PCR, to see if SMN1 is present. We're also doing the same type of testing in newborns, and actually as of just a few months ago, we are now performing newborn screening in all 50 states in the United States for SMA. So, this is actually old news. Recently there are two states, the last two states, actually, started screening for SMA. So, all babies in United States are now offered newborn screening for SMA and we look for SMN1. If SMN1 is present, then it's considered a negative test. Of course, some of these patients might still have SMA because they might other types of mutations, but typically that's not picked up on a newborn screen.

So, the algorithm earlier would tell us how to diagnose those patients who do have an SMN1 gene by doing sequencing, which would identify point mutations for example, which is found in about 3 to 4% of patients. There are also some other types of mutations that could occur. We typically also do SMN2 copy number. Now, this is not necessary to establish the diagnosis of SMA, but it is considered as a standard of care. It's routinely done, and it does help us predict how severe the SMA will be in our patient.

I would like to point out that we no longer suggest doing things like muscle biopsy, EMG, if SMA is suspected. It's not necessary to do an EMG, although some of these patients who are mild may have already undergone an EMG. A CK is not necessary for making the diagnosis of SMA, and a brain MRI, which is very common to be ordered in all neurological patients, including SMA, is also not necessary.

Now let's talk a little bit about SMA patients, their psychosocial, psychological and social well-being, as well as their caregivers. So, SMA does have a significant burden of disease. Adults and young adults with SMA talk about this lack of independence and the significant disease burden. And this was more prominent among non-ambulant patients, obviously, because they're less independent. SMA may also limit a patient's ability to engage in social activities. These limitations may result in social isolation and may contribute to depression and anxiety, which can be based on the perceived stigma of disabled persons and emotional impact of these social interactions. So, significant psychosocial impact is a common theme across multiple studies of patients with spinal muscular atrophy and their families.

So, some potential challenges include navigating challenging systems like Social Security, Medicaid waivers, personal care attendance, which may be absolutely necessary for some of our patients, insurance challenges, and durable medical equipment, which is often either downplayed or not approved or deemed not medically necessary, sometimes. And these patients, you know, many of them with the appropriate accommodations can actually be very productive, functioning members of society. Many of them go to college and many of them actually work, and they do need these accommodations to be able to do so, however. So, they need accessible housing and work environment, and it's important to help these patients advocate for their personal needs, such as personal care attendance and other reasonable accommodations.

And the other thing is that, you know, traditionally it's really the pediatric specialties that have been taking care of these SMA patients, and that's going to be a challenge in the future because this is now an aging population with better longevity. And so, we're actually going to see a growing population of SMA patients, and the pediatric specialties are really not going to be able to continue to accommodate these patients. And we really need to be able to find transitions into adult specialists, and this includes a number of different specialists, like GI, pulmonary, cardiac, as well as PT/OT and nutritionists. And we have to improve access to mental health services because of the issues that I discussed earlier.

So, it's important to hit all of these points. Encourage, navigate and support. We're talking about encouraging autonomy and maximizing independence. Address needs with home, work and social life, and identify goals to connect to resources. It's also important to navigate the care decisions. There's emergency care planning, for example, advance care directives, and legal and finance financial care planning.

And it’s important to support the parents as they adjust to their role, empowering patients’ independence, but continue to offer support for parents. The parents are the primary caregivers, encourage options for additional support.

So, let's talk about disease-modifying therapies. We'll cover some of the safety and efficacy of these FDA-approved therapies and what it looks like in adults with spinal muscular atrophy. So, there are a number of different factors to consider when we're choosing these options; age, the type of SMA they have, the severity, basically, the indication, how it's listed in the prescribing information, the safety information for each drug, how to monitor, how it's administered, and the takeaway points from the clinical trials.

It's kind of neat to show this because this pipeline is something that's published on a regular basis by Cure SMA and this has really evolved. What's shown here in blue are the approved therapies, and you can see there are a number of therapies that are still being investigated. And it really wasn't that long ago when there were no approved therapies and everyone was kind of watching this like this was some kind of race to see which drugs would get approved soonest, and what to look out for. And now we are talking about three approved therapies that are available on the market.

So, the first FDA-approved therapy was in 2016, that was nusinersen. All these drugs increased the amount of SMN protein in lower motor neurons. There is a narrow treatment benefit window, the earlier we treat the better. Of course, they could still be treated later in the course of the disease, and they do benefit, but they benefit less. So, better outcomes are seen with earlier use, but treatment delay is common because sometimes patients get diagnosed later, they have milder disease and it's underappreciated, or they perhaps are not sure, they're hesitating whether they should go on treatment, questioning what the benefit of the treatment would be. There's also patients who really have later onset disease, so it's hard to identify their disability until much later in life. And there’s also denial of the parents or family members when they're seeing their child.

So, here are the three different therapies. There's nusinersen, which is an antisense oligonucleotide. This is injected intrathecally directly into the spinal fluid. And there are 4 loading doses and maintenance doses every 4 months. There's also risdiplam, which also has a somewhat similar mechanism action by modulating splicing. So, these two drugs modulate splicing. This is a small molecule and can be given orally and it reaches systemic tissues, although the most important tissues of course of the spinal cord. And this is a daily oral drug.

And finally, this is onasemnogene abeparvovec is a gene therapy. So, it's an AAV viral vector delivered gene therapy. And so, the payload is the SMN2 gene, and so we call this the SNM trans gene. And this is FDA-approved for only children less than 2 years of age, and this is given intravenously. It is a single one-time therapy.

Here are some safety considerations. There's thrombocytopenia, coagulation abnormalities and renal toxicity, which may be seen with nusinersen. Risdiplam may have some teratogenic effects as well, and there are some drug-drug interactions, particularly MATE drugs that are cleared through the MATE transporters. And with gene therapy, there is a potential for acute liver failure, a systemic immune response, thrombocytopenia, thrombotic microangiopathy, as well as some troponin elevations, which may be some type of myocarditis.

So, these are the adverse events that have been reported in these clinical trials.

And the monitoring that is shown here, you can see that there is some blood tests as well as urine analysis that's performed, urine protein in particular for nusinersen. For risdiplam, the only thing that we need to monitor is the body weight, because it's a weight-based dosing. And there's a significant number of tests that are typically monitored for gene therapy in the first 3 to 6 months when the patients received therapy, and they're all listed here.

We're not going to be talking as much about gene therapy because that's not something we can give to adults. So, onasemnogene abeparvovec, this is the recombinant AAV9, so that's adeno-associated virus type 9. That's the capsid, so it's carrying the transgene. It's being delivered to the motor neurons. It's to promote survival of the motor neurons by expressing SMN protein.

The way nusinersen and risdiplam work is they change the splicing behavior. So, as I showed you earlier, exon 7 is often excluded from the SMN2 gene, but if you can change it so that SMN2 includes exon 7 at a higher frequency, that would actually result in more SMN protein being expressed. And with more SMN protein, that would actually result in improved motor neuron survival.

Listed here are some other drugs that are still under investigation, which may or may not be beneficial to patients with SMA.

So, I showed you earlier, here, this is the SMN1 gene and the SMN2 gene, and the fact that patients who have SMA, they're missing the SMN1 gene, so the only SMN protein that they're able to produce is made from the SMN2 gene. But of course, that's only made at about one tenth the efficiency of what the SMN1 gene would do, so it does it at a much lower efficiency. So, again, the idea behind nusinersen and risdiplam is it modulates the splicing behavior. So, instead of having this 90 to 10% ratio of truncated versus full-length messenger RNA, what we have here is the drug changing and shifting so that we have more full-length messenger RNA resulting in

higher levels of functional SMN protein. And with higher levels of functional SMN protein in motor neurons, the motor neurons will survive longer, and so that helps to change the disease modification, it has a disease-modifying effect on patients.

So, there have been a number of studies, double-blind, placebo-controlled studies performed in patients and that led to the approval. But very importantly, that data was done mostly in children, so appropriately, when these drugs were approved, there were a lot of questions that were asked about whether these drugs really work in adults. And I don't think that there was ever really any doubt that they worked in adults, but there was some question of how much benefit they might have. And so, here's some of the data that has actually been collected and accumulated and reported since nusinersen has been approved.

This is one study that was published out of Stanford using a scale they called the CHOP INTEND, but basically, they were looking at motor function among patients who were receiving nusinersen. And what you can see here is the trend was that patients who were receiving nusinersen, in general with time, they should improvements in their motor function. So, this is one of the studies.

This is another study that was published out of Germany. These are what we call waterfall plots and what they – so, basically what they're doing is plotting all the patients in the study that they captured at the 6-month timepoint, at the 10-month timepoint, and the 14-month timepoint. And so, these numbers are a little different because it's an ongoing study. There are fewer patients who were further along than the patients who were 6 months out, so it's – But nonetheless, what you can see here is each individual patient is a different line. Some of these patients had no change. The patients were doing the best is ranked over here on the left, and the patients were doing the most poorly are the patients that are shown over here on the right. And what you can see here is that that there are a number of patients who had no change, there was a good number of patients that actually improved, and there are some patients that seem to be declining.

Now, one statement I think that you can make is that there appears to be more patients that are improving than patients that are declining. And in fact, if you ask how many patients were either stable or improving, that was actually most of the patients, probably close to somewhere between 80 to 90% of the patients were either stable or improving. And that's an important point because you would not expect in this disease, which is progressive, for patients to improve. You know, they might be stable, but most of them would be declining with time.

And if you look at the 10-month timepoint and the 14-month timepoint, what you can see is the number of patients that are improving really starts to increase with time, and the number of patients that are declining actually decreases. And if you ask the question, what percentage of patients were either stable or improving, it really is most of the patients, more than 90% of the patients shown here. And if you draw a line that says, well, what percentage of patients had at least a 3-point improvement, and this is what we would define as the clinically meaningful difference or change, it's 28% exhibited at least a 3-point improvement, and then 10 months later 35%, and then 14 months later 40%. So, there really does seem to be a trend that the patients who are longer on therapy actually seem to be improving.

Here is another study that was published showing that patients who were on therapy and were able to walk at the beginning of the study actually improved in their ability to walk the 6-minute walk test, showing the distance that was walked in 6 minutes. So, after their 6th visit you can see that there was an increase, which is statistically significant in the distance that was walked in 6 minutes.

Here are some quality-of-life assessments and you can see that the quality-of-life assessments generally were improving as the number of visits increased, so the time on therapy. And there's some P values showing here the various different domains in these quality-of-life, some showing more improvements and better P values than others.

Let's talk about the risdiplam. So, this is the oral therapy. So, there isn't much real-world data. All we have are the clinical trial data. This is from the clinical trial that the sponsor called SUNFISH. And so, SUNFISH Part 2 had a double-blind placebo control study, and what you can see here is in the patients who were receiving risdiplam versus placebo, you can see there was a statistically significant and clinically meaningful difference in this other motor scale called the MFM-32 showing that patients who were on risdiplam were doing better than patients who were on placebo.

Here's some of the safety information and you can see that risdiplam was generally well tolerated. If you compare these most frequent adverse events across these different adverse events, you can see that the, you know, percentages are generally comparable, and you can look at the parentheses actually shows you the percentages. So, it's generally well-tolerated with mostly mild to moderate in severity adverse events.

What's also interesting though is, what is the mechanism of action. And so, with risdiplam they were able to measure how much SMN protein was actually being made and they could compare between before and after they started treatment. So, with risdiplam, looking at the blood levels in these patients, and these are just different populations within this one particular study, but what you can see is in general, they were showing an increase in the amount of SMN protein that was being made in the blood. And so, this is likely reflective

of being used as a surrogate marker to predict approximately how much SMN protein was being made in the spinal cord. And so, generally speaking, we're seeing like a 2-fold increase in the amount of SMN protein after patients go on risdiplam.

But coming back to the SMA patients themselves, we have to talk about overall management, and really, they are in – many of these adults are really in a chronic phase of their disease. And so, we are not expecting really dramatic improvements, dramatic meaning we're not expecting patients who have never walked for several decades start walking, but they might exhibit some improved motor function, such as, you know, moving their hands better, being able to type better for longer periods of time, for instance, being able to function at work, setting up and using a mechanical typewriter instead of a screen typewriter, screen keyboard. These are all clinically meaningful differences for these patients and these types of changes are more realistic than expecting somebody who's never walked to start walking. So, it's important to set these realistic goals and expectations, and then try to maximize their long-term motor outcomes, and that really requires a multidisciplinary care team to address each patient's unique needs. You know, everybody has different mobility needs. Everybody has different orthopedic needs, respiratory needs, nutrition and psychosocial needs. And it's important to improve access to providers who have experience with treating adults with spinal muscular atrophy.

And this is taken from a publication that was actually number years ago. Sumner published these. And this is really a conceptual curve looking at motor function. So, let's say a normal person may have this curve and Type 1, Type 2 and Type 3 patients might have these types of curves showing you that patients may reach a chronic phase of their disease. And if you were to pick one of these curves, let's say over here on the right, let's say a Type 2 patient, or if that patient who's destined to be a Type 2 patient. If you treat them early in the course of the disease, you may make them really a different type of patient, possibly, you know, a Walker, even if they were supposed to have been a Type 2 patient. Whereas if you treat it a little bit later, their benefit may be smaller, OK, and maybe they wouldn't be walking, but they would still be a better functioning sitter. Whereas if you treat late in the course of the disease, there could still be significant benefit, but that benefit would be a lot smaller. So, really treating early is really going to benefit patients the most.

So, how do we maximize long term motor outcomes using disease modified therapies? Well really, it's giving them the proper therapy, that's directing exercises that, you know, assess the needs that the patient has, improves their strength and flexibility on maintaining mobility, optimizing body mechanics and minimizing orthopedic complications. And orthopedic interventions may still be needed, and they should be used appropriately.

So, the multidisciplinary management is there to address the patient's individual needs. They have to be assessed and then intervene if appropriate. So, pulmonary management for any respiratory insufficiency is important. If they have hypoventilation, they may need pressure support. So, some type of PAP support, and airways clearance might also, be appropriate, and that could come in the form of what we often call catharsis, or insufflation/exfoliation devices.

And intervening for obstructive sleep apnea for upper airway obstruction. Gastrointestinal, as well as nutritional interventions may be necessary. These patients have specific nutrition needs and also have motility issues that need to be addressed. And then there is, of course, important interventions that may be necessary for swallowing as well as speech and communication. Bone Health is an issue, and of course the psychosocial issues that I've brought up in the past. But it's important, again, to increase the capacity for adult SMA care. With these disease-modifying therapies, there will be improved longevity and there will be an increase in the population of adults with SMA. And so, really, transitions of care from pediatric to adult providers will be needed to accommodate this population. Adult patients also have multidisciplinary needs that really differ from the pediatric patients with SMA. It's really best addressed by adult providers. So, there really is a growing need for healthcare providers to care for adults with SMA.

So, here are the key summary points as I come towards the end of my talk. Patients with SMA need care plans that are individualized and evidence-based. They need to incorporate shared decision model as these patients need to have the independence to make their own decisions. We have to address psychosocial needs and integrate available disease-modifying therapies into their care.

There are FDA-approved therapies that aim to increase SMN protein production, particularly in motor neurons where the disease is most active. And when considering disease-modifying therapies for adults with SMA, the latest safety and efficacy data of available and emerging agents needs to be factored into this decision.

OK, so, at this point we have reached the question-and-answer section. So, let me take a look. One of the questions is: What is the age range for adult onset SMA? How late can they present?

So, that's a good question. I think the oldest undiagnosed SMA patient I have ever seen was in his 30s. And so, he was just having some mild difficulty walking, and actually, he had mild difficulty running. He used to be able to run, but he started to struggle running. And many years ago, we probably never would have thought he had SMA but, you know, because SMA testing has become increasingly more available, you know, we had done a number of tests first and it really looked like it was a motor neuropathy with, you know, denervation. And we tested a neuromuscular panel and the SMN gene was deleted. And he had 4 copies of SMN2, so it turns out

that he does have adult-onset SMA, so we would call him Type 4. That's my experience. I'm sure there are probably even other patients that might be milder, but those are actually exceedingly rare.

Do you have any suggestions for overcoming some of the insurance barriers patients face?

Well, I think that's why a multidisciplinary team is helpful, because a multidisciplinary team has a lot more – and this is a team that specializes in SMA – they have a lot more authority experience with SMA patients. And so, when we argue that this patient needs this type of equipment, or this needs this type of drug, or needs this type of intervention, insurance companies tend to pay attention to who is actually ordering this and they tend to approve it more than if it's a provider who has very little experience with SMA. So, that's why it's helpful to have centers of excellence, so-to-speak, that are taking care of SMA patients. And, you know, there aren't that many adult centers of excellence and so, part of what I hope is that there will be a growing number of centers that can become centers of excellence taking care of SMA patients. And some might even be places where multidisciplinary care is already being provided for other diseases and can, you know, some of those elements can then be transferred over to SMA patients.

What percentage of intermediate SMA patients progress to severe in its natural course?

So, yeah, I would say that intermediate SMA patients is a trajectory and they're all progressing, they're all pretty much deteriorating if they're not treated. So, a sitter is a sitter. I've seen sitters lose the ability to sit. I've seen sitters start off being able to feed themselves and then they reach a point where they're not able to feed themselves because their arms are so weak. And so, you know, these are very large categories to say their sitters or their walkers. A sitter is many times, they're still deteriorating significantly and that affects their independence, and it affects their quality of life.

Do you anticipate the availability of the disease-modifying therapies increasing the number of people with SMA or reaching adulthood and having children, and then in turn, increasing the prevalence of SMA overall?

So, that's an interesting question. I think what you can say is that with the availability of genetic testing, you know, I don't think that we're going to see a huge increase in SMA patients because a lot of patients, you know, who know that they are carriers for instance, may undergo pre implantation genetic diagnosis and perhaps select for embryos that are less likely to have, or not likely to have, SMA. So, of course, any SMA patient who has a child, their child will most definitely be a carrier. They will most definitely have a mutated copy of SMN. And so, that's not avoidable, but that grandchild – so, if that child has a child, then you can avoid that grandchild from being affected through prenatal diagnosis.

Are there any potential blood biomarkers to monitor muscle function improvement?

This is a really good question, and we do actually have markers that we think are very, very promising and meaningful. There's actually neurofilament light chain, which has become very popular in monitoring how much the motor neurons or other types of neurons are deteriorating. And so, what we are seeing is that patients who are untreated have higher neurofilament light chains than patients who are treated, suggesting that we have really slowed down or stopped the for the deterioration of motor neurons.

As I always say, it's kind of like, you know, a patient who has muscle disease, a CK. You know, so if you have high CK that seems to indicate that there's a significant ongoing muscle damage. Likewise, if there's significant ongoing motor neuron deterioration or degeneration, then the neurofilament light chains will be higher and so, that's probably a biomarker which will become more commonly used in the future. It's really only become commercially available very recently. I think you can order through some of the commercial labs now, but it used to not be available.

How do you find patients and families respond when bringing up transitions of care to adults? Any tips for addressing this transition?

So, there's a lot of anxiety that comes with transitioning to adult providers because these patients are very worried about whether their new providers will know anything about SMA and what those needs are. And that's a fair concern. But I mean, I think that nonetheless it doesn't mean that they shouldn't transition. They really should transition, and these providers, you know, maybe some of the people in the audience will end up learning a lot more about SMA and being able to treat these patients. And that's what I'm hoping will eventually happen, that we will have providers step up and provide multidisciplinary care for SMA patients.

Do we know what would be the cost of this treatment after covered by insurance?

So, these treatments are generally well-covered by insurance. I have not heard of patients complaining that they have a large copay that they have to pay. So, I don't think that that's really been an issue for our patients. There's probably some copay assistance programs that come with this.

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