SMA: Clinical Aspects, Diagnostics and Follow-Up

June 7, 2018

Transcript

Funke Akinsola: Good afternoon, everyone. Thank you so much for joining us for the first installment of the spinal muscular atrophy webinar on clinical aspects, diagnostics, and follow-up.

Funke Akinsola: I just wanted to say that the webinar is funded by CDC but the contents are solely the responsibility of the authors. They do not necessarily represent CDC or Department of Health and Human services. Now, I will hand it off to our Moderator, Patty Hunt from Texas Department of State Health Services.

Patty Hunt: Good afternoon, everyone. Thank you for participating in today's webinar. As Funke said, this is part one of a two part series on spinal muscular atrophy. The webinar is geared towards those who are and may be responsible for screening, diagnosing, and treating SMA. The series was developed with expert guidance from the APHL QA/QC subcommittee and in collaboration with the Newborn Screening and Molecular Biology Branch at the Centers for Disease Control and Prevention.

Patty Hunt: Today's speaker, it gives me great pleasure to introduce Dr. Jennifer Kwon. Dr. Kwon is an associate professor of neurology, pediatrics and pathology, and laboratory medicine at the University of Rochester Medical Center. She received her medical degree and Masters in public health at the University of Michigan. She completed her residency in pediatrics at the University of Pittsburgh and her residency in child neurology at Washington University School of Medicine.

Patty Hunt: Dr. Kwon has a strong interest in improving long-term clinical outcomes in children diagnosed with rare disorders by newborn screening. She is a consultant for the evidence review committee for the Secretary of Health and Human Services Advisory Committee for Heritable Disorders in Newborns and Children. She's a member of the American Academy of Neurology Registry Committee overseeing the Axon Registry, a registry for clinical performance in outcome improvements for neurologists and has been working to develop and improve long-term follow-up registries for patients diagnosed with rare neurological diseases by newborn screening. Welcome, Dr. Kwon.

Jennifer Kwon: Thank you. I decided to pitch my talk as if I were speaking to medical students and teaching them about spinal muscular atrophy for the first time. I'm sure that there are people who are listening and who know quite a bit about this topic but this is going to be a little bit on the introductory level but if you have

any questions, feel free to ask. My understanding is the questions will be held till the end of the talk. Next slide.

Jennifer Kwon: I have received funding from Sanofi Genzyme because I'm the site PI for the Genzyme rare disease registry and they've also paid for some travel expenses. BioMarin, I've provided some information about the process of newborn screening for neurologic disorders. As was mentioned, I'm also on the evidence review work group for the advisory committee. My comments are my own and should not be taken to reflect the reviews of the evidence review group or any other federally-sponsored agency. Next slide.

Jennifer Kwon: Spinal muscular atrophy is an autosomal recessive disorder that affects lower motor neurons in the spinal cord and brainstem. It results in progressive motor weakness and atrophy. Next slide.

Jennifer Kwon: When we talk about lower motor neurons, it's because, simplistically, I think of a motor signal that starts in the brain, as it begins in the brain and goes through the first neuron, which is the upper motor neuron. That neuron ends in the gray matter of the spinal cord and interfaces with the lower motor neuron. This interface occurs at many levels. That's what the diagram of this spinal cord is just meant to show. Spinal muscular atrophy is not a disorder of the brain or the upper motor neuron. These children are cognitively normal. They are simply extremely weak because their lower motor neurons are not functioning well. Next slide.

Jennifer Kwon: Spinal muscular atrophy also has a fairly broad phenotype. It can begin anywhere from early in infancy up through adulthood. The range of severity is variable, depending on the age of onset. The clinical course is variable. We talk about muscular atrophy, we talk about the types of SMA. These are primarily distinguished by the severity of muscle weakness and the age of symptom onset. Types I and II are the most severe. Typically, when I talk about how do we distinguish Type I and II clinically, I say, "Well, Type I patients are those patients who will never sit. They will never get beyond being able to lie on their back and maybe move their arms and legs while lying on their back whereas Type II patients are those infants who are able to get to sitting. They're robust enough to look relatively normal during their first six months of life but then begin displaying weakness. Next slide.

Jennifer Kwon: To give you a sense of the story that goes along with these types of SMA, I'm going to present a typical case that we see in child neurology practice. This little girl, Maria, was the second child to her parents. The pregnancy and delivery appear to be normal. These are experienced parents because they have had one other child. They did not think that there was anything particularly unusual about Maria. She was admitted at age of three months because she had a cold that she just had difficulty managing. She was entering into respiratory insufficiency and required intubation, which is very unusual for a viral illness in a three-month old.

Jennifer Kwon: On her examination, she was very interactive, had a social smile, tracked well. She was immediately … Let's just say all of the nurses and staff just immediately fell in love with her. She also had pretty prominent head lag and was unable to lift her legs off the bed. She could not lift her arms up at the shoulder but she could lift her forearms off the bed and she could grasp with her hands. These are the exam findings of the child who has pretty significant proximal muscle weakness. She was able to be extubated after two days.

Jennifer Kwon: When we spoke with the family about why they didn't really think up till three months that she had any difficulties, part of what they said was that they had noticed her head lag and they had noticed that she was maybe a little bit behind her brother but they thought of him as this very robust, muscular baby and she just seemed like a different personality. They really thought it was more her temperament and because she was so cognitively impact, it took them a while to realize that she had significant muscle weakness.

Jennifer Kwon: We were able to make the diagnosis shortly after that hospitalization. By six months of age, she was unable to feed well. They knew that this was part of her diagnosis of spinal muscular atrophy. We think of it as a progressive disorder but another way to think about it is that children have a certain amount of strength. As they grow, they really outgrow the strength that they have and the ability to keep up with their nutritional needs and their pulmonary needs.

Jennifer Kwon: When, at six months of age, she was unable to feed well, the parents did agree to artificial nutrition via G-tube but they were also entering into discussions with palliative care and other providers about the kind of life they wanted her to have because they did not really want her to be on a life of artificial pulmonary support. She died at age 10 months because she was unable to keep up with her pulmonary needs. Next slide.

Jennifer Kwon: I apologize. This slide had some pictures in the background of it. What this picture showed were photos of infants who were less than six months of age who you would be able to see are quite weak. I think you could probably intuitively tell that without significant artificial support, such as the support the child that you're seeing has, they would not be able to survive for very long.

Jennifer Kwon: In fact, the natural history of children with spinal muscular atrophy Type I is that they die before age two years. Typically, they die around age one year. That's the age that they stop being able to really be able to feed themselves by mouth at all. They do need to have airway and pulmonary support. This is a boy you can see that he has a permanent tracheotomy. He's on probably around-the-clock ventilatory support. You don't see his G-tube but he must be getting artificial nutrition. Next slide.

Jennifer Kwon: I spent some time talking about the story of SMA Type I because that is one of the more common forms that we see. The other common form is SMA Type II. These children are relatively robust during the first few months of life. People start maybe noticing some weakness but they're hitting the major milestones.

They're able to roll and they're able to sit up on their own but it's after that families realize that their children have significant weakness.

Jennifer Kwon: These children are never able to stand or walk. Fairly quickly during their toddler years, they require a wheelchair to help support their spine and also to help them get around. These children at a remarkably young age learn to steer their wheelchairs. It's quite remarkable to see a three year old driving quickly down a hallway. They're all very bright. They can expect to have feeding issues and pulmonary issues but we generally see these patients as surviving into the late teenage, early adult years, even if they don't get a lot of intervention.

Jennifer Kwon: Nowadays, with barely standardized and aggressive interventions early in life, these children generally graduate high school as well as college and possible graduate school. They are, however, very weak as you can see by the older child being lifted into her wheelchair by her mother. Next slide.

Jennifer Kwon: Children with SMA Type III do attain the ability to stand and walk. It's variable, the amount of time it takes them to come off their feet but by their teenage years, they often have great difficulty ambulating on their own. They use a wheelchair for longer distances. They are stronger than children obviously with SMA Type I and II. Their life expectancy is much longer. They are expected to live well into adulthood. Next slide.

Jennifer Kwon: Those are the three major types of spinal muscular atrophy we talk about. The question is why is there so much clinical variability in this disorder? We know that nearly all types of spinal muscular atrophy are caused by bi-allelic deletions of a gene called SMN1 or survival motor neuron one. These mutations, these deletions are inactiving and absent and SMN1 makes SMN protein and absence of SMN protein is lethal.

Jennifer Kwon: The variability in presentation is because these children also possess a gene called SMN2. SMN2 is an imperfect copy of SMN1. On its own, it does not create SMN protein unless it is aberrantly processed. The SMN2 pre-mRNA can lead to an SMN1 transcript if a mistake is made in the pre-mRNA processing. This is one of these situations in which an abnormal gene that is abnormally processed can turn into a normal transcript. Two wrongs do a make a right in this situation. Next slide.

Jennifer Kwon: This is, in diagram form, pretty much the same thing I said. All of us have one copy of SMN1 on each of our alleles. We also have variable numbers of copies of SMN2. SMN2, this is a region of chromosome 5 that is chock full of deletions and duplication so we can have several SMN2 copies. The more copies we have, the more likely we are to have normal SMN proteins.

Jennifer Kwon: Just going through the diagrams created by John Kissel and his colleagues, SMN1, which is often known as telomeric SMN, creates a transcript that is translated into SMN protein. SMN2 creates a transcript that, because of the

mutation that interferes with splicing, results in a truncated SMN protein, which is really not active. However, 15% of the time, the transcription process is in error and the error results in a normal SMN protein. New slide.

Jennifer Kwon: Just to quickly classify how we think about the two types, all of the types result in absent SMN1. SMN1, we've highlighted with a blue color. None of the patients who have any of the types of SMA have the SMN1 gene but they may have different copies of the SMN2 gene. In general, the more copies that you have, the stronger that you are. In general, you could say that a child who has two copies of SMN2 and with absent SMN1 is likely to have Type I SMA. If they have three, they're more likely to have Type II. If they have more than three, they're likely to have Type III or even IV or V. Next slide.

Jennifer Kwon: This makes diagnosing spinal muscular atrophy a fairly straightforward. Spinal muscular atrophy is typically diagnosed now using DNA-based testing. All commercial labs provide the SMN1 deletion results. The typical result is that there is a homozygous deletion. They also provide the SMN2 copy number, which allows us to give a sense roughly of the prognosis and type of SMA the patients likely to have. While the copy number is associated with motor function, knowing SMN2 copy number's still not sufficient to accurately predict the SMA type in pre-symptomatic children. That may be confusing because I just said that they do tend to correlate and they do but it's not a perfect correlation. Next slide.

Jennifer Kwon: This slide, this algorithm comes from the diagnosis and care guidelines that were recently published for spinal muscular atrophy. They appeared in February in neuromuscular disorders. It's a very helpful article, except, interestingly enough, it does not include discussion about newborn screening because that's how rapidly the world of spinal muscular atrophy has been changing but you can see that in their algorithm of diagnosing SMA, it starts with having the clinical suspicion of SMA. Then, you go directly to SMN1 deletion testing.

Jennifer Kwon: As I told you, most of the lab that provides the information about SMN1 deletion also tell you about the SMN2 copy number. This is the current protocol that we use for diagnosing SMA. I'm just looking. We do in neurology, and actually, I would say in general pediatrics as well, the clinical diagnosis and the clinical suspicion of SMA if you've seen a case, it's probably not that hard to think about it. Then, that's why more and more, rather than having a diagnostic odyssey, we tend to go straight to SMA testing but if it turns out not to be a clear-cut case of SMA but another cause of weakness. Of course, there's another pathway that we go down. Next slide.

Jennifer Kwon: I told you that there was a rough correlation between SMN2 copy number and the type of SMA that you have. We know that, in Type I patients, they can have one, two, or even three copies of SMN2. Remember that the way we assign an SMA type is really based on a clinical criteria, the age of onset and really how weak they look.

Jennifer Kwon: Most children with one SMN2 copy so they clearly have SMN1 homozygous deletion so they have spinal muscular atrophy but they have only one SMN2 copy. Both infants are often severely weak at birth and may not survive the first month of life. Typical SMA Type I patients have two SMN2 copies. It's unusual but some children may have three and yet still present very early with their weakness.

Jennifer Kwon: SMA Type II patients generally present between 6 to 15 months of age. As I told you, Type II patients are able to sit so they have that degree of strength to get them through infancy. They can also vary in terms of the number of copies of SMN2 they have, anywhere from two to four.

Jennifer Kwon: Then, the other column to the side that I should point out is that SMA Type I patients constitute about half of the patients that we see. Their natural history, their lifespan is less than two years. SMA Type II patients have the next most frequent, are also frequent. They're about .2% of the total SMA population. Their lifespan is often to early adulthood.

Jennifer Kwon: SMA Type III patients typically present after, like in their second year of life so between 12 to 24 months. These are children who are able to walk. They're often not walking normally. They may present to clinicians because their walking seems odd but they usually have more SMN2 copies three or four. I was surprised to see that they constituted a quarter of the patients who present with spinal muscular atrophy. I previously thought that Type II patients were more common. These are children who are fairly robust and we do expect a near normal life expectancy for them.

Jennifer Kwon: Type IV patients, we think of as rare. These are patients who not only are able to walk but they seem actually fairly normal through much of their childhood. They generally are fit to present in adulthood. They have four or five SMN2 copies. New slide. Next slide.

Jennifer Kwon: Not to belabor the point about SMN2 copies but it is, of course, the one piece of prognostic information we have. We have been looking at SMN2 copy numbers from a number of different angles. This is a paper that just came out this year in which a group looked at the Spanish population of SMA patients. They looked at them in a number of different ways but one way they looked at these patients was to divide them by clinical type, types one, two, and three. Then, look at the number of SMN2 copy numbers, how they were distributed within those clinical types.

Jennifer Kwon: They also, as you can see from the title, looked at more than 2,800 reported cases in the world. They did a similar type of analysis but in general, the analysis of the smaller group of Spanish patients is pretty consistent with what they found in their worldwide cohort.

Jennifer Kwon: Again, if you have Type I SMA, you're most likely to have two copies of SMN2, and if you have Type II SMA, you're most likely to have three copies, so you may also have two copies. Then, if you have Type III SMA, you can have three copies or four, but you can obviously, if there are a few who have just two copies. New slide.

Jennifer Kwon: The presence of the SMN2 copy and the fact that we knew that aberrant processing of the pre-mRNA transcript could lead to a normal SMN1 transcript. That lead to the development of the drug nusinersen. Drug companies had already been aware of the potential of antisense below the nucleotide to allow them to alter the pre-mRNA processing of these transcripts to create, to modify, basically, the abnormal genetics of various disorders. It became obvious that this technology of antisense-oligonucleotides could be used in spinal muscular atrophy. Basically what they're doing with their ASO is they're creating a setting in which all SMN2 transcripts are basically converted to SMN1 transcripts. Next slide.

Jennifer Kwon: This is actually a dramatic set of videos. I'm not showing the videos but I'm going to tell you how to find them. If you search on YouTube Cameron, SMA, and nusinersen, you'll see that the journey of this boy Cameron, whose family learned, when he was just under two months of age, that he had spinal muscular atrophy. He was started at that time, he was enrolled in one of the early nusinersen trial. It shows how he responded to the drug and how his disease course was so markedly different than the natural history of SMA Type I patient. Next slide.

Jennifer Kwon: Again, some of his earlier photos I can't show but what you can see is at 20 months of age, he is standing. He doesn't require any airway support or chronic ventilatory support. He is able to be fed by mouth. This is, I would say, for a child neurologist, nothing short of miraculous. Next slide.

Jennifer Kwon: Nusinersen, this antisense-oligonucleotide is also interesting because, as I told you, that the place where these patients need to have SMN protein, the place where they need to have an intact SMN1 transcript is in their anterior horn cell of the spinal cord. The natural cite, then, for providing this antisense-oligonucleotide is in the spinal fluid.

Jennifer Kwon: These children simply receive via lumbar puncture, a dose of nusinersen or this antisense-oligonucleotide. This side, then, is meant to show first just how lumbar punctures work, where the needle is inserted, which is in the fluid-containing space that is below where the spinal cord ends. The next side is meant to show you CSF flow. Our spinal fluid is always circulating. As soon as the five ml dose of medication is infused into the patient, the CSF flow mechanics just simply takes the drug and circulate it throughout the spinal cord. Next slide.

Jennifer Kwon: This is one of many images that have been shown by Cure SMA and other advocacy groups to argue for the incredible benefit that can be gained from this

treatment. On the one side, you see Cameron standing at 20 months of age. On the other part, you see the natural history of Type I spinal muscular atrophy, which is that if you don't die between one to two years of age, it's because you are being maintained on artificial ventilatory support and often, nutritional support.

Jennifer Kwon: This is the boy who was diagnosed at four months. It said that he was put on permanent ventilation at five months after his first cold. He's never been able to sit up, swallow or move, versus Cameron who was diagnosed early and treated with nusinersen or Spinraza early and now can sit unassisted and stand. Next slide.

Jennifer Kwon: I don't know that too many drugs like nusinersen have been seen. Once the early results from the clinical trials were reported in 2015 or '16, the company, Biogen, applied for FDA approval. It was granted in December of 2016. Even though the initial trials only looked at patients with Type I SMA, the FDA approved nusinersen, also called Spinraza, for all types and all ages of spinal muscular atrophy. I can only assume that was because of the truly amazing results that we're seeing in the Type I population.

Jennifer Kwon: Also impressive was the price of the drug. Each infusion of nusinersen is $125,000. In the first year, the period of the loading dose, that adds up to $750,000 of drug in the first year and $375,000 for the drug annually. This drug needs to be given for the lifetime of the patient. I should say that once nusinersen is loaded and is of sufficient concentration of spinal fluid, it only needs to be given every four months, which is why the price tag is $375,000 for the drug. Next slide.

Jennifer Kwon: We immediately knew that this was going to be a barrier to treatment for patients with spinal muscular atrophy. We also, we being the medical community, weren't sure how well we could manage the needs of SMA patient who have more chronic forms of SMA or who have had SMA for a very long period of time. Even though the FDA felt that they were eligible for getting the medication, we weren't sure what the effects of the medication would be.

Jennifer Kwon: I would say that there was a lot of information we didn't have, though we were optimistic that this medication would be helpful for all forms of spinal muscular atrophy. I'll add that, as I told you, there are patients who have much milder forms of spinal muscular atrophy. While they're fortunate in that they don't have severe weakness, it also raised the question about when these patients should be started on treatment. Next slide.

Jennifer Kwon: Those are some of the questions that clinicians, that we've been asking. We're still trying to come up with information to help guide ourselves on the treatment of patients who have had spinal muscular atrophy for a while but as you know, newborn screening is being advocated. There are clearer treatment guidelines being established for patients who should be getting Spinraza or nusinersen.

Jennifer Kwon: When it was clear that spinal muscular atrophy newborn screening was going to be nominated and discussed, Cure SMA put together a working group to discuss treatment and management guidelines in patients who identified by newborn screening. The working group, I apologize. It should say the working group, unanimously recommended to have all patients who were likely to have Type I and II SMA be treated immediately, that is, as soon as they were diagnosed. The assumption is that that would be within the first month or two of life but because we can't tell who's going to clinically develop Types I and II, we had to rely on the laboratory information so the recommendation was that early nusinersen treatment be provided in all infants with two or three SMN2 copies. Next slide.

Jennifer Kwon: This is the figure from another paper from this year, which is really a write-up of the SMA newborn screening treatment guidelines from that Cure SMA sponsored work group. What they said, just walking you through the flow chart, is that if you have newborn at screening and you have a positive screen, then the confirmatory testing should include evaluating SMN2 copy number.

Jennifer Kwon: I'll just start at the top. If you have only one copy of SMN2, then it is likely that the patient has what we are now calling Type zero SMA or very weak Type I SMA patient. These patients may already be so weak and their lower motor neurons already be so denervated that they may not benefit as much from treatment with nusinersen. The recommendation is that if you only have one copy of SMN2 that there be discussions between the family and physician about whether or not to start treatment.

Jennifer Kwon: If you have either two or three copies of SMN2, then the recommendation is that the infant be treated because they will probably have either Type I or Type II SMA. If you have four copies of SMN2, it is likely that you will develop Type III or IV and, therefore, it may be reasonable to wait to treat and to begin treatment at the start, when weakness is first noted. Next slide.

Jennifer Kwon: The one obvious question to have then with those recommendations is how many patients are we talking about who have two copies or three copies? This is a bar chart from the Calucho et al paper that described the Spanish cohort of SMA patients.

Jennifer Kwon: If you look at the second bar, which are the patients who have two SMN2 copies, they had 266 patients who have two SMN2 copies. The vast majority of them, 88% of them, had Type I SMA. Then, if you look at the patients who have three SMN2 copies, about two-thirds of them either have Type I or Type II. A third of them will have Type III SMA, which is the type where these children are relatively strong during their first year of life. They are able to walk but their walking may not be that normal and they cannot go from walking to running and they can't sustain their walking. They come off their feet at some point but that's usually a bit later in childhood. I think this paper is a very interesting and helpful paper. The graph is rich, as well. I'm happy to go back to it if anyone has any questions about it but why don't we just go onto the next slide?

Jennifer Kwon: This all sounds great. We have a disease that really needs to be identified early in life. It needs to be identified pre-symptomatically and there's a form of the disorder, Type I SMA, in which treatment before six weeks of life would be optimal. All of those things are a clear-cut reason for why we should be screening newborn for spinal muscular atrophy.

Jennifer Kwon: But we also live in an era where we are surrounded in medicine by extraordinarily expensive drugs. I would say nusinersen is almost in the category of its own in terms of how very expensive it is. This is how our current US medical system reacts to highly expensive medical drugs.

Jennifer Kwon: In general, these are not drugs that are given in an in-patient setting. We need to figure out how to give them in an out-patient setting. That has to do with the fact that in-patient care, whether you're a child or an adult, the cost tends to be a bundled cost. That ensures that you to just paying one set fee for a diagnosis, whereas in out-patient care, you can bill for the entire cost of a medication.

Jennifer Kwon: However, even if you can do that in the out-patient setting, these drugs are never fully reimbursed by any insurer and certainly not by Medicaid. It can be very financially risky to store these high-cost drugs in hospital pharmacies. In general these types of drugs can quickly cause deficits in hospital pharmacy budgets. That has to do, again, with a payment system that we have in the US. There are all kind of things that make hospitals very nervous about administering nusinersen. Next slide.

Jennifer Kwon: This is a drug that has to be administered in a hospital setting. The second issue that we haven't discussed before when we're discussing children who are very young is the fact that many of the individuals that we're treating now for spinal muscular atrophy are, again, those who've had it for a while and because they are so weak, their backs also are weak. A weak back becomes curved and undeveloped scoliosis. Many of these individuals need to have back surgeries so they have hardware in their back or they have curvature of their back. Both of these things, hardware and curvature make a lumbar puncture very difficult. The second hospital-based barrier is just simply where are we going to do this procedure? What kind of specialized setting is this procedure going to be done in? Next slide.

Jennifer Kwon: This is just an example. This is a patient who obviously does not have spinal muscular atrophy. You can see a very straight back. They are about to do a lumbar puncture in a radiology suite under radiologic guidance. This is a common way for us to treat these patients and infuse nusinersen in patients who are older, who've have spinal muscular atrophy for a while. This is probably not going to be the case for patients who identify by newborn screening who will be infants who are getting these lumbar punctures. That procedure is more straightforward and can be done in pediatric treatment centers. Next slide.

Jennifer Kwon: Even though I said that we can infuse nusinersen in a variety of settings in the hospital so pediatrics clinics have their own settings. The interventional

radiology, sedation areas, those are all other settings in which we can provide these infusions. The fact is that it's often not that easy to access those places. For the past year, since nusinersen has been introduced, every hospital has been trying to figure out in their own environment, in their own way how best to administer this drug. That is another, I think, layer of difficulty in terms of providing this treatment.

Jennifer Kwon: The look and also even though infants may not require sedation, for example, for administration of the drug, as these children grow, there's no question that we will need to provide sedation. It's just too frightening a procedure for children not to have it. Adding sedation is yet another layer of complexity in terms of providing treatment. For, I think, nearly every center that provides this drug, there are ongoing stories of the amount of coordination and discussion that has had to take place between different groups just to be able to pull all of the required people together to administer this drug. Next slide.

Jennifer Kwon: Then, this is just an example of the loading infusion schedule. When you start a child on nusinersen, you have to make sure that you have a certain number of days blocked off to complete the loading cycle. Next slide.

Jennifer Kwon: Finally, it's a concern that we all have that not every child is going to end up being able to be treated. Then, another way of saying it is that to create a reasonable business plan for treating spinal muscular atrophy in a given medical center is likely going to mean that some children with spinal muscular atrophy will not be able to be treated because hospitals have to make decisions about how many children with poor insurance or less optimal insurance can be treated in their centers. I think those are discussions that we've not yet had with the recommendation that SMA be screened in newborns. Next slide.

Jennifer Kwon: As I said, there were two papers that came out recently, both regarding the recommendations for the care patients of spinal muscular atrophy. I will refer them to you. They're both in neuromuscular disorders. One is on the diagnosis and management of SMA. There's part one and two. The first one's about the diagnosis, rehabilitation, orthopedic and nutritional management. The other has to do with pulmonary and other management. Next slide.

Jennifer Kwon: To summarize this paper, I would just say that these experts are recommending that proactive and regularly scheduled PT, orthopedic, pulmonary, and nutritional care are really necessary in order to lead to better outcomes. These are patients that should be followed by neuromuscular specialists or MDA clinic specialists every three to six months, especially for Type I and II patients. Next slide.

Jennifer Kwon: Then, this is a slide that I always like to put in. The background is just a landscape of newborn screening in the US in 2012. It's a bar chart that shows the first bar is organic acid disorders, PKU and other amino acidopathies, all the way through the most common disorder that we screen and ends up being diagnosed via newborn screening is hearing loss.

Jennifer Kwon: What is the impact of SMA likely to be? SMA is in the blue box and it is likely to have numbers around 400 diagnosed a year by newborn screening. Those numbers are roughly similar to, let's say, all children who are diagnosed with fatty acid oxidation disorders, just to give you a sense of the impact. Next slide.

Jennifer Kwon: My final thoughts and summary is just that spinal muscular atrophy, as I said, is a disorder of lower motor neurons. Most patients present with severe weakness and early death. We have a treatment, nusinersen, which offers great benefit to those with Type I and Type II SMA when given pre-symptomatically. Nusinersen is still a new drug. We have much to learn about who should optimally receive treatment and when this treatment should start and when it should or ever stop. Then, the final slide. Oh!

Patty Hunt: Thank you, Dr. Kwon. Did you have any additional closing remarks?

Jennifer Kwon: No, no. That's fine. I thought I put in another slide but I didn't so we'll just end there.

Patty Hunt: Thank you very much. That was very good overview. We are now beginning the question and answer section of the webinar. You can ask questions in two different ways, either through the chat box or you can unmute and ask question in person. Press star seven to unmute.

Patty Hunt: Funke, do we have any questions in the chat box during the presentation?

Funke Akinsola: No, not yet.

Patty Hunt: Okay. While we're waiting for any questions to come in, I really appreciated, Dr. Kwon, the hospital one on one that's a whole different side that sometimes we really don't think about, so appreciated hearing all of the intricacies of what is probably coming down the pipeline.

Funke Akinsola: We do have a question in the chat box. It says, "What do we know about the risk to Type III patients who are receiving this treatment early?"

Jennifer Kwon: I would say the one thing that I didn't stress is that this seems to be a very well-tolerated drug. There is a lot of stuff that we have to do just to get the child in a position so that we can do a lumbar puncture and infuse this medication. It's a teaspoon of liquid that's infused. I have not seen anyone have any kind of adverse effect from the medication itself.

Jennifer Kwon: In general, if you were to ask me, I've not seen any problems with sedation either but I would expect that we would have more issues related to sedation, more minor adverse effects related to sedation than we would from the infusion of this medication. I think the risk for Type III patients would be very small.

Funke Akinsola: Great. Thank you. The next question says, "With the high prevalence of carriers for this disorder, detecting carriers may be overwhelming for newborn screening programs. How is it for newborn screening programs to detect carriers?"

Jennifer Kwon: I'm probably not the best person to address that. I think that the next session will be more on the nuts and bolts of now newborn screening for this disorder should work.

Jennifer Kwon: My understanding is that many states are looking at screening options in which they don't detect carriers for all the reasons that I'm sure you're thinking of. Their preference would be just directly detect those who have [homocidis 00:53:28] deletions and then just refer those infants on for confirmatory testing.

Funke Akinsola: Thank you. We have a couple more questions in the chat box. The next one says, "How do you expect the cost of treatment to change over time?"

Jennifer Kwon: The cynic in me does not expect the cost to change over time. I guess I think that Biogen is gambling that this is going to be such a sought-after treatment that people will pay and they will ask their insurers to pay. So far, that does seem to be the case.

Funke Akinsola: Thank you. Next question says, "By the time symptoms present in otherwise asymptomatic cases of SMA, has irreversible damage occurred?"

Jennifer Kwon: That's an excellent question. I would say that some irreversible damage may have occurred. If you think about the lower motor neuron, when it starts not working and weakness sets in, there may be a period of time in which that lower motor neuron can be salvaged but, for example, the child that you saw who had the tracheostomy in place and look like they are essentially quadriplegic. That child probably has very few viable lower motor neurons in place. The lower motor neurons that were working are probably never going to work, no matter how much they're infused with SMN protein.

Jennifer Kwon: The rationale for providing this drug, even to patients who seem almost end stage is that if it looks like they have any motor neurons working at all, this drug is likely to maintain those motor neurons but to get back to your question, the onset of weakness does imply that lower motor neurons are in great distress and may be dying or have died.

Funke Akinsola: Thank you. The next question says, "Do the cost of the treatment reported include just the cost of medication or are those reported costs inclusive of the hospitalization and procedure?"

Jennifer Kwon: That's another excellent question. The cost that you hear about of the drug are just the cost of the drug. The insurers that are being asked to pay for this drug

are also being asked to pay large sums for the sedation suite, involvement of radiology, people like me who do the infusions, that those are all separate costs.

Funke Akinsola: Thank you. The next question says, "What are the other benefits of early identification of SMA besides being able to infuse this medicine in the pre-symptomatic phase?"

Jennifer Kwon: I think that it can be valuable for families to know early of the diagnosis because there are other interventions, other pulmonary interventions, therapy-related interventions that may help slow what we think of as the natural progression over time but I would say that, to me, it's the fact that there was a treatment that really drives us to wanting to identify this disorder in newborns.

Jennifer Kwon: I will say, when I say, "Us," I am not a neuromuscular specialist. I am not somebody, as fond as I am of my patients with SMA, they're not a cohort of patients that I've devoted my life and career to. I think people who have probably see many more advantages to having early diagnosis but to me, I think it's really the treatment that drive the rationale for newborn screening.

Funke Akinsola: Thank you. We just have a couple more questions in the chat box so we'll be rounding up shortly. The next one says, "Is anything known about the long-term effectiveness of the drug? Is it still as effective after several years of treatment?"

Jennifer Kwon: Nothing is known about the long-term effectiveness of the drug. We only started these clinical trials a few years ago. We haven't even been able to see how these children are doing past the age of three.

Funke Akinsola: Okay. Next question says, "Do you know where gene therapy trials are at and the likelihood of gene therapy replacing these infusions?"

Jennifer Kwon: That's a very good question. I don't know the answer to that but it is certainly much discussed and everyone feels that it's been our future but it's in an immediate and almost graspable future. I've not heard anything like gene therapy will be available in a year or two years but the results are so very promising. I think people are hopeful that it will be present in the next few years.

Jennifer Kwon: That gets back to the question about will the cost of Spinraza ever go down. I think that's really probably the biggest motivator for Biogen to keep the cost where is it because gene therapy is likely to make Spinraza obsolete.

Funke Akinsola: Thank you. The next question says, "What are they typical annual costs of an untreated SMA PACE patient, for example Type II?

Jennifer Kwon: That's an excellent question that I don't know the answer to that.

Funke Akinsola: No problem. The final question, "Has the Health and Human Services secretary responded to the recommendation to add SMA to the rest?"

Jennifer Kwon: I would definitely refer to the APHL on that one.

Funke Akinsola: Thank you so much for your time, Dr. Kwon. Thank you, everyone, for joining us for today's webinar. I'm going to hand it over to Patty to wrap us up.

Patty Hunt: Just a big thank you to Dr. Kwon for agreeing to present this very valuable information today. That was a wonderful presentation. Thank you to all the participants.

Patty Hunt: Part two of the webinar series will be on June 28th at the same time. It will concentrate on the screening methods. We'll hear from several states and their experiences in introducing screening for SMA.

Patty Hunt: The webinar is recorded and will be archived in the APHL website along with all the previous webinars. If you get a chance to take a look, we have many archived webinars for previous topics.

Patty Hunt: PACE credit is offered for each webinar. To obtain your PACE certificate. Participants can complete the brief evaluation and get a 1.0 credit hour for viewing the webinar today. PACE credit can still be obtained after the archived webinar is posted. Thank you very much, everyone, and have a good afternoon.

Jennifer Kwon: Thank you. Bye.

Funke Akinsola: Thank you.

Patty Hunt: Thank you.