Dr. John I. Takayama: Hello, and welcome back. I will now introduce our next speaker, Dr. Althea Shelton, is Associate Professor of Neurology and Pediatrics at Vanderbilt University Medical Center. Since 2011, her research and clinical focus have been on sleep problems in children and young adults with neurodevelopmental disorders. She is a sleep physician in the Vanderbilt Multidisciplinary Prader-Willi Syndrome clinic, and she previously served as the onsite neurologist for the Autism Treatment Network. Finding innovative ways to treat sleep problems in patients with neurodevelopmental disorders and improving the quality of life for them and their families is her overarching goal. She will now discuss sleep in children with neurodevelopmental differences.

Dr. Althea Robinson Shelton: Hi. Thank you so much for inviting me. I will be discussing sleep problems in children with neurodevelopmental differences and how to individualize the approach, so a modified approach. I have no conflict of interest. These are my objectives. I want you to be able to recognize sleep disturbances that commonly occur in neurodevelopmental disorders, understand management strategies for treating these sleep disturbances, and to describe ways to modify one's approach to assessing sleep problems in patients with neurodevelopmental disorders. I'll intermittently say NDD instead of neurodevelopmental disorders. Sleep disturbance is quite common and it's a common concern for caregivers of individuals with NDD. It's been reported that the prevalence of sleep disorders in people with developmental differences is as high as 86%, and sleep disorders in children with NDD commonly last into adolescence and adulthood, unlike their typically developing peers. They also occur at a much higher rate than their age match typically developing peers. Sleep disturbances are included in the diagnostic criteria for many developmental disorders. Why a modified approach for children with neurodevelopmental disorders? Assessment of sleep in children with NDD presents unique challenges, and that's due to a couple of things. There are communication difficulties, there can be a host of co occurring conditions, and there can be an altered sensory processing or sensory experience. For the child, there're just overall an increased prevalence of chronic sleep concerns that you wouldn't see in a typically developing child. They have vulnerabilities that make sleep concerns more multi factual in nature, underlying medical comorbidities, not being able to communicate what's going on with themselves. Then there's potentially more significant and challenging behavior in response to common approaches. We have this ideal approach that we read in our sleep books that may not actually work for children with neurodevelopmental disorders. But there are also caregiver factors. There could be shame and defensiveness. A parent feeling shame when their next door neighbor makes a joke because their 9-year-old is still co sleeping with them. There could be apprehension that providers don't really understand the complexity of their child's profile. This compounds the stress that they're experiencing. But we also have to remember that if their child is not sleeping, then they're not sleeping. They are experiencing all the things that can happen with sleep disruption and sleep fragmentation. They're sometimes just holding on barely. Then they get concerned that there's this history of recommendations that they've already received from other providers, from their primary care provider that highlight this ideal rather than explain some realistic deviations that may be needed that explain supports that may be needed. That success may look different for them than it would look for a typically developing child. Really, also, they are concerned that we won't individualize the recommendations that we have. This is a review article that I wrote on sleep disturbances with NDD. What I really want you to get from this is, in this article, I focused on a particular set of disorders that I primarily see. One disorder can present with multiple different sleep disturbances. For instance, patients with Prader-Willi Syndrome, which is a genetic disorder due to deletion in chromosome 15, is one of the known causes of genetic obesity. They have a high prevalence of sleep disordered breathing about 80% of the time. But what many people don't know is that even when you treat the sleep disordered breathing, they can continue to have excessive daytime sleepiness because they have hypothalamic dysfunction. But people still focus on, well, it's the weight. It's their obstructive sleep apnea that's making them sleepy and not looking to see if there could be other sleep disorders going on. You may have a patient with autism that is experiencing sleep onset insomnia and sleep maintenance insomnia, but maybe the sleep maintenance insomnia is

caused by obstructive sleep apnea or nocturnal seizures or their sleep onset is not behavioral at all, but due to untreated restless legs that they can't tell you about. The pathophysiology of sleep disorders and sleep disturbances is multifactorial. When you look at NDD in particular, there are factors that play a more prominent role in the underlying pathophysiology, and that includes neurobiological factors. Those play a big role, and that's a whole another lecture. But when you have a child with a particular genetic deletion, that deletion itself can lead to underlying sleep disorders and make them more prone to underlying sleep disorders. There are psychiatric co occurring factors, in particular, the one I think about right now is anxiety and anxiety preventing sleep onset. Medical disorders, epilepsy, GERD, constipation, all of these things can compound a sleep disorder and worsen a sleep disorder. Then there are family dynamics. Is it a single parent household? Are there multiple children with disabilities in the household? Does mom and/or caregiver work second shift and thus will not be able to implement what you're giving? Does the child stay at grandma's until 8:00 P.M. Till mom comes to pick them up and they live 45 minutes away, so they don't really get home. The bedtime you're telling them is not really going to be realistic. With all that said, one of the things and one of the first articles I give to our sleep fellows. I'm the program director for sleep fellowship is this article that came out in 2010 that's still very relevant about the five finger approach to looking at therapy of sleep disorders and in the evaluation of sleep disturbances. Therapeutic success in patients with neurodevelopmental disorders really depends on the recognition of comorbid conditions that may manifest as sleep complaints. Or as specific sleep complaints can be secondary to a number of sleep disorders. A parent could come to me and say they're waking up multiple times at night and they've been told that it's due to behavior, but maybe they have underlying sleep disorder breathing, even though they're not snoring, or maybe they have excessive periodic limb movements that are waking them up at night. Maybe even though the seizures are controlled, they may be having subclinical seizures. I like to think about things. I love this five finger approach where your thumb is your circadian misalignment. This is when you're going to get a careful history of their sleep wake scheduling, including their weekend scheduling. What do they do as they're preparing for bed? What do they do on the way to bed? Who's involved in putting them to bed? The index finger representing pharmacological factors. In this population, we know that they have a high burden of medical and psychiatric comorbidities, and they often have polypharmacy. Did they start a new medication? Does one has the dose of a medication been increased? Has the dose of their Lamictal been increased? Lamictal is activating. Maybe the Lamictal is now causing some sleep onset insomnia. The middle finger representing medical comorbidities, such as we talked about constipation, which is chronic in my population of patients that I see, GERD is another one. The ring finger is psychiatric and psychosocial factors. We talked about anxiety, but there could also be depression. There could be psychosis. Then, of course, then just after you've addressed all of that and looked at all of that, then we go and look at primary sleep diagnosis in addition. It's really important in this population that you have a broad differential. I'm mentioning that because so many times the apprehension that I see from my first visit with a caregiver is that they don't think anything can be done because this is just due to their autism, this is just due to their behavior. But I always put behavior at the end. It's in the differential diagnosis, but it's at the end, and I put a big, broad differential of what could be occurring. Then really don't forget a detailed family history. This has helped me so many times. Yes, I've had anemia or grandma has restless leg syndrome. There's a big history of iron deficiency in the family. Everybody in the family has obstructive sleep apnea. Getting this detailed family history is really important. I can't go over all sleep disorders, but we're going to go over three sleep disorders that you'll often see in this population of patients. We're going to start with insomnia, and this is a big one, so we're going to go really fast. I like to think about things in buckets. When I'm giving a prime a goal of my sleep recommendations, I always start with telling the parent or caregiver, give, communicate, and prepare. We want to give the child as many cues as possible to distinguish between night and day. For instance, using visual schedules, which I love, a visual schedule for the daytime and a visual schedule for the nighttime. Giving concrete expectations of what we do during the day and what we do at night. Not just saying this one time, but you may have to repeat this every day, multiple times

during the day, and then preparing a child's body for deep continuous sleep. What I often see is there's no preparation. Well, I told them five minutes. Five minutes is so vague for many children. Then I told them, turn the tablet off and go to bed. But no real preparation, no calm down time, no wind down time. When you're talking to the parent then about implementing the recommendations that you're going to give, you really have to distinguish to them between what's ideal and what's realistic. They may have a older sibling that is typically developing that the traditional methods, the traditional sleep recommendations worked wonderfully for them. But this may not work for their child. I always caution the patient the parent that once we have insomnia under control, If anything in the environment changes, if you guys go to vacation, you may have to start over at the beginning again because that's a change, and that change may disrupt what we've started. It's really important that you look at multiple interventions because just one type of intervention may not work. Then also use evidence-based supports to help this go well. We talked about routines and habits. A daytime habit schedule is one of the things I recommend. What is my morning schedule? What am I doing today? Today, I'm going to school, and you want to consistently implement this type of schedule. You let them know we're going to come out of our sleep environment, wake up and then come out of our sleep environment, out of our sleep clothes into areas of light. Bright light increases production of serotonin. Sertonin is a precursor of melatonin. If we experience bright light when we first wake up and have increased serotonin production, this potentially may help us sleep better at night. Some amount of movement in the morning and just consistent timing and avoiding snoozing. I have this little visual clock, which is on all iOS and Android devices and great for children who don't understand the numbers of the number time. But one of the things I hear parents say is, I do tell them 5 minutes before bed, 10 minutes before bed. But even as adults, that's so vague. Oh, my God, 5 minutes has gone by already. Using this kind of a visual and letting them know, hey, TV time ends in 5 minutes and I set a visual schedule, the visual timer, or I set a regular timer that they can look at, and then we're going to begin wind down time. Wind down time may look different for them. It may include something to help them self-regulate like we would do in occupational therapy. Sometimes I even do things such as wall push ups or bear crawls. It may be a more active wind down time than you would think. Then once we're going to bed or getting ready for bed, we also have this bedtime habit calendar, and this is going to look different for every family. It may change, may be somewhat similar, but it could be different for every family. Because when I think of a home, I think of the culture of the home. There are different cultures in the world, but every home has its own culture. As providers, we cannot put our own beliefs on what we think that home should be like. We need to know what the home is like and try to make our recommendations fit into that. When I think about electronics, this is a very big thing like screen, screen, turn off the screens. The traditional advice is to stop electronics 30 to 60 minutes before bed. But there are studies now that are coming out. This one is the one I'm going to talk about a little bit, where it shows this one looked in particular at autistic adolescence and it showed that for them, quiet technology actually helped to wind them down. This cut the screens off immediately may not work. Also, if you have a parent saying, this is the only way I can get them to sit still, if I take it away, they're going to have a tantrum. They're going to run around, listen to that. Then we have to then incorporate the screens. Ways that you can incorporate screens is Number 1, I always say no YouTube videos, those four minute videos, seven minute videos, and every time the video changes, there's going to be this dopamine spike. Find something boring to watch Bluey, a nature documentary, but something that's prolonged, nothing that's quick or too much lights or flashing lights or different scene changes. No Michael Bay. He's a director that does transformers and has a lot of lights and flashing and bombs. You want to decrease the volume and the screen brightness, make sure if we are now not having the screen right up to our face. If it's a tablet, it's further away. If it's a TV, it's further away, you may, at the end, just want to mute and add white noise. Sometimes I talk to a family, and they can't even imagine not having a TV in the room. I used to be this zealot. You must take the TV out the room. Then I realized that for many people, they've always had it. The parent grew up with a TV in the room. The concept of the child not having a TV in the room seems almost impossible. Well, maybe instead of taking the TV out of the room, one way to

signal that it's bedtime is we mute the TV and put a white sheet over the TV. Now we can't look at the TV per se, but we've not taken out the TV. We are working with the culture of their home. Gradual extinction, fading is something I use very commonly, but sometimes we go too fast with our fading. Fading may actually be much slower than you think. The first step in fading is finding out what is the parental presence of the parent? Are they sitting in the room? Are they sitting on the bed? Are they laying on the bed? Are they laying completely cuddled up with the bed? With the parent, the child. Because then the first step, if they're just all entangled together, may be, you know what? We're going to work on him falling asleep without you holding him. That's the first step. Then once he can fall asleep without you holding him, maybe the next step is you're going to sit on the bed and have him fall asleep that way. Once he can sit on the bed, then you'll sit. Once he can fall asleep that way, you sit in a chair close to him. Instead of saying, well, just walk out and wait outside the room for a minute and then come back in, if the child is used to this constant contact of a parent, that may be very jarring and it's not going to work. Fading may need to be done much more gradually than you thought taught or you think. Why do we end up doing pharmacological interventions? Behavioral interventions are a primary thing for patients with insomnia. You want to address sleep hygiene. You want to try to change that behavior. But there has been a few studies, but this, in particular, metasynthesis of which looked at eight systematic reviews, 38 studies in total. It looked at sleep-based interventions in children with ASD ages zero to 18. It found that just behavioral interventions, only 25%, if we just did behavior, it was only successful 25% of the time. Really what they found was a combination of behavior therapy and melatonin was that showed the most improvement and that melatonin may be effective for sleep initiation and sleep maintenance. I know melatonin is a hot button topic right now, and I think the issue is it's not been used safely. In many other countries, melatonin is a prescription. In my opinion, melatonin should be used under a under a doctor's with a doctor's advice and helping them along the way. Oftentimes, I have parents come in and they don't know they show me a bottle and it's not just melatonin, it's melatonin with Benadryl. Or I've had patients come in and they tell me they're giving their 77-year-old 60 milligrams of melatonin and I tell them, who told you to do that? They just think, well, more is better. Melatonin really should be used under a physician supervision. There's really no reason for a typically developing child to be using melatonin. But oftentimes in patients with new developmental disorders, they may need an aid in sleeping. That's the first one that I use. I start the lowest I can, so 0.5 milligrams if they've never been exposed to it, but oftentimes they have been exposed to it, but they've not used it in the right timing. It should always be 30 minutes before we're laying down to bed, not at 6:00 P.M. Where I often see it being given. This Bruni O, et al. sid a systematic review of studies looking at melatonin use in different genetic syndromes and the melatonin dose that was used and whether there was improvement in sleep. Then you can see that there was improvement in sleep with melatonin use up to 10 milligrams. The other thing is I never go over 10 milligrams. If 10 milligrams is not working, it's not going to work. Whenever possible, you're going to choose a medication. If we are going to have to do a prescription medication, you choose a medication that will treat something that's co occurring. If a patient has epilepsy, first of all, I may talk to their epileptologist to see if we can increase the nighttime dose of their epilepsy medicine or anti seizure medicine. If they have anxiety, maybe I'll consider using a sedating antidepressant, such as doxpin and you start very low, lower than you think you would need to start and go very slowly if you are going to start something.

Speaker 1: Pardon me, Dr Shelton. It's five minute warning for you.

Dr. Althea Robinson Shelton: Thank you. When we think about pharmacological treatments, you look at whether they have epilepsy. Think about antiepileptic medications, bipolar, you're going to look at irritability, and then anxiety, consider sedating medications. We're going to go over quickly restless legs. We're all aware that restless legs is a clinical diagnosis, and you can apply the adult criteria to neurotypical adolescence. You have to have the urge to move. Rest brings it on. It gets better with movement, and in the evening, it worsens. It can happen during the day, but it worsens in the evening or starts in the evening. This classical clinical presentation is how someone who's

neurotypical in adolescence would present and would be able to tell you this in their own words. But you have to remember that it's not age, but language and cognitive development that determine the applicability of restless legs diagnostic criteria. In the diagnosis of restless legs in a child requires that they be able to describe this in their own words. You may hear a child say something completely different. They don't know what the word urge is, so if you say you have an urge to move your legs, they won't be able to answer you. But do your legs feel funny? Do you have a need to move your legs? Oftentimes they may say worms or pinching or tickling your alleys. The reason why I'm talking about restless legs is I oftentimes have children who are minimally verbal or nonverbal, and what I'm hearing is I'm getting a history and mom and dad keeps saying they're getting out of bed, running back to me and I'm asking, well, are they saying anything during this time? Are they touching anything? Some times I hear, they're saying aww or hurt. By the way, I have been trying, I go and rub their legs. Well that rubbing of their legs is counter stimulation, the same stimulation that the adult does or the typically developing adolescence does when they walk. You can't say definitively that they have restless legs, you can say that they have possible restless legs or probable restless legs. But really, it is something I put high in my differential when I have a child who is consistently showing bedtime resistance. Some supports. This is why it's important to have a good family history, is if they are first degree family relative restless legs. Is there history of iron deficiency, anemia in the family? Also, I do often get a PSG. Although when you look at the ASM guidelines, a PSG is not needed for the diagnosis. But if I get a PSG and I see that there are elevated periodic limb movements, it gives me a higher suspicion that there is restless legs. This was a study going back and looking at kids with autism, and they had chronic insomnia, and there were 103 kids identified. When they go back and look through the charts, really, it wasn't just chronic insomnia, about 39% of these cases met the diagnostic criteria for restless legs or were sometimes later diagnosed with restless leg syndrome. The observed movements that most correlated with restless legs were leg kicking in the bed and body rocking. Sometimes you have to ask, if they are staying in the bed, what are they doing? What are their legs doing in the bed? What is their body doing in the bed to suggest that it may be restless legs? This really is a ferritin issue. The other thing I want to point out is that the most important thing is to get not just a prick, an iron prick or CBC. Those are the last things to decrease, but really looking at iron stores, so serum ferritin, yes, fasting is ideal I rarely get it fasting. But In these patients, I get a ferritin and I'm looking for to see if the ferritin is less than 50. Sometimes I hear, my PCP told me it was normal. Well it can be in normal range, but if it's less than 50, there's a good chance that there's still going to be a brain iron deficiency because your body is going to judiciously delegate. Ferritin is your bone marrow stores of iron, it's a protein that gets converted into iron. Your body is going to judiciously delegate where that goes, it's going to send it to the red blood cells first, and so you may not still be getting the iron to where it needs to be. If the ferritin is less than 50, that's when we treat. So 50 is normal, but we're still going to treat it. I'm going to quickly go over obstructive sleep apnoea. The pathophysiology in many of our patients will present with sleep disordered breathing, and many of our patients have hypotonia, and this is weakness of the respiratory and upper airway muscles. What I hear from many of my families is they don't snore. But maybe because their tone is lower, what their snore sounds like is a completely different thing. We need to have a high suspicion of this, could this possibly be obstructive sleep apnea and look at other underlying ways that it may present. I talked about some patients with neuromuscular weakness like low tone, which many of our genetic disorders have. Many of our genetic disorders of unknown significance have, and so they may not snore, but they may be very restless, they're flopping like a fish. They may sleep with their neck hyperextended, or they may sleep slumped over. They may just present with multiple night awakenings. If I have a child presenting with multiple night awakenings, my first question is, what is waking them up? Is there an underlying sleep disorder waking them up? Then what keeps them up is their ADHD or underlying anxiety because they have autism. But what's waking them up? Secondary nocturnal enuresis. The book says secondary, meaning they were dry and then they began to have bed wetting. But oftentimes I see that they just never stop having bed wetting. If they are still wearing pull ups or some type of diaper at night, I ask, what is the pull up looking like? Is it just slightly wet or

is it overflowing and we're still wetting the bed. Sweating at night, headaches upon awakening, nausea upon awakening, and so you need to ask different questions to this population. Yes, snoring, gasping, choking, but the answers to those may all be no, and they could still have obstructive sleep apnea. Then behavioral problems are highly associated with excessive daytime sleepiness. If I have a parent that's seeing their behavior is changing, I'm in clinic, my patient before me, what mom said, she's 11-years-old on the autism spectrum, I'm worried about her mood and behavior. I probably have run over, but I have these other slides that talk about treatment options and how to treat. Not just adeno tonsillectomy, but other surgical interventions, and then in particular, consider also medical and dental therapy. Things like myofunctional therapy, rapid palate expansion, especially if you have a child with a high arch palate, which many of our kids with neurodevelopmental disorders do, and so you have other options to treat obstructive sleep apnea. Then I just wanted to put that there are future possible treatments,. Hypoglossal nerve stimulator has been approved, but there's also now a possible medical therapy. In conclusion, the pathophysiology of sleep disturbances in neurodevelopmental disorders is multifactorial. When you look at neurodevelopmental disorders, there are changes in dysregulation in sleep biology that play a big role in this underlying sleep disturbances. The clinical presentation of sleep disturbance is really a amalgamation of all these co-occurring conditions. Then you're going to need varying interventions that may be required to treat sleep and behavior problems in children with developmental disorders. I have some other resources for you guys at the end of the slides. Talking about iron, different evaluations that you can use to assess, and then different websites that you can send your families to to get handouts. Thank you very much.

Dr. John I. Takayama: Dr. Shelton, thank you so much for a very comprehensive discussion, and I would say that the prevalence of sleep disorders probably is so high in this population that we should be doing screening all the time.

Dr. Althea Robinson Shelton: Yes.

Dr. John I. Takayama: Yes. The home environment does seem to play a role, and as you talked about the gradual extinction, and it seems like there's many steps involved in the tailored treatment and that it will require some level of trial and error, maybe. How do parents respond to recommendations about try this and see if it works, try that if that doesn't work?

Dr. Althea Robinson Shelton: I think you have to sometimes gauge where the parent is at because sometimes I have a mom that comes in and we sit down and she has tears in her eyes already. With that parent, I'm not going to say, let's try all of these multiple interventions. This may be a parent that I give one thing to try, but we also have to maybe go ahead and start medication in this child until we can get their sleep, get them sleeping, get mom sleeping. Now when I see them back, we can start implementing more behavioral changes. When they're sleeping and feeling better, they're more apt to try these behavioral interventions. You leave the room because some parents are just not at that headspace where they are able to implement it. Or maybe someone has passed or they just lost their job, and it just may not be the time. But if it is, most parents are willing to try, and we're very fortunate that we also have a psychologist. She's a psychologist for autism treatment network, but she does a lot, will help a lot with behavioral intervention. I will start the behavioral intervention and the talk, and I'll often refer to her to help with quick follow up and continuation.

Dr. John I. Takayama: Thank you. One question and then the others I was wondering if you could answer offline, which is sleep safe beds for children on the spectrum.

Dr. Althea Robinson Shelton: Sleep safe beds for children on the spectrum, they are great, but they're often hard to be covered by insurance. I will tell you that most insurances do not care if the child has challenging behaviors or may harm themselves or they're eloping. None of those things will get that bed approved. What they're looking for is an underlying medical issue, and so oftentimes what I focus

on if I'm trying to get a sleep safe bed for a child is the fact that they may have epilepsy, and this would help. Or they're on a CPAP, and so they're on respiratory intervention, and it's important for them to stay in bed. But there has to be some type of underlying medical issue for those beds to be approved. But I do like them if you can get them approved.

Dr. John I. Takayama: Thank you again, for us, for an amazing talk.

Dr. Althea Robinson Shelton: Thank you for inviting me. I really do appreciate it.