Dr. John I. Takayama: Dr. Bhooma R. Aravamuthan is an Assistant Professor of Neurology and Director of the Cerebral Palsy and Mobility Center at the Washington University School of Medicine in St. Louis. As a systems neuroscientist and pediatric movement disorders specialist, she conducts translational research on dystonia, pathophysiology, and cerebral palsy. She is passionate about disability equity and lifespan cerebral palsy care and serves as the Disability Equity spokesperson for the American Academy of Neurology. Her research is funded through multiple sources, including the NIH and the CDC. She is married to an epileptologist and is a mom to 8-year-old twin boys and a 6-year-old girl. Dr. Aravamuthan's presentation is on evidence-based approaches for spasticity and dystonia management in people with cerebral palsy.

Dr. Bhooma R. Aravamuthan: Thanks so much, John. I appreciate that introduction. I'm excited to be here and listening to these talks. They've all been illuminating, and I hope I can follow and provide some insight to this audience. I'm excited to talk about tone management in CP, and I want to make sure I take a lifespan perspective to this. These are my disclosures, non-relevant to the talk today. In talking about tone management, spasticity and dystonia management, I wanted to start off by talking about how to think about CP in the first place, how to conceptualize when to manage tone and how to manage tone i.e., goal driven care, and then the importance of differentiating between spasticity and dystonia and how that drives care, and then how to think about that in people across the lifespan and things to look out for with people with CP as they age. First, how to identify CP? Cerebral palsy is a very common condition. In the US, estimates currently range from 2-3 in 1,000. Worldwide, that's about four in 1,000. These estimates are comparable to the prevalence of Parkinson's disease, and CP is the most common lifelong motor disability. The cost estimates are out of date, but over a decade ago, the CDC estimated that for any group of people born with CP in a given calendar year, that their lifespan, medical and associated costs exceeded a million dollars, and I'm sure that number has inflated since then. Because of the prevalence and the cost, this is a medical imperative and a socioeconomic imperative as well. You may know that the definition of CP is currently undergoing a revolution or an evolution, and there has been quite a lot of interest in a group that I collaborate with with standardizing how to define CP. In brief, the framework that we are proposing is that CP is a lifelong neurodevelopmental condition that affects functioning and is due to atypical brain development, causing some motor sign at less than age two without loss of motor skills by age five, and that loss of motor skills can be predicted or observed. That predicted portion is pretty important because what we know is that the earlier you identify CP, the better. The reason for that is that institution of early interventions, early therapies, early tone management is the only condition modifying option that we currently have in use for CP. The earlier you diagnose, the earlier you're able to initiate the CP-specific therapies a person needs. These papers were landmark works by the Australian registered group led by Iona Novak, and they're both available at the QR code that I've linked here. Ways to diagnose early include using a set of referral criteria. These are criteria that were established by an international Delphi called the prompt referral criteria. I'm not going to go through them in detail today, but I want you to know that they're available, and they're easy go to guides to think through whether we should refer someone for formal evaluation for CP or make sure that we're highly vigilant for a CP diagnosis and clinic. Another tool is something called the Hammersmith Infant Neurological Examination, which has been well validated to be able to pick up on CP early in children as young as three months old. This is the brief Hammersmith Infant Neurological Examination. It's one page long. I love the hind in large part because of these wonderful stick figures, but also in large part because a lot of the examination maneuvers you do on the hind are things that you would do to assess a young child anyway. The brief HINE, again, is only one page long. There are validated age-based cutoffs for when to refer for a CP diagnosis, and both the prompt criteria and the HINE criteria are again available as a one pager that you can print out in this QR code in the corner of the screen. I'd encourage you to use those, incorporate those criteria in early diagnosis of CP efforts in your clinical practices. With those sorts of definitions in mind, I'm going to walk through a couple of scenarios in people at different ages. The pitch is, does this person have CP or not? This is a 10-year-old kid who was born preterm, has motor delays, but no regression and has spastic hemiplegia.

Obviously, this is a very limited set of findings for this person, and there's much more that you would likely be able to know with the direct evaluation. But overall, there is nothing here that is a red flag in terms of this not being CP. This child very likely meets criteria for a CP diagnosis. They have an etiology that would cause an atypical brain disturbance. They have motor delays without regression, so they're not losing any skills, and they have findings on exam that are associated with that atypical brain development. This next person is a 50-year-old. They have trouble walking that began in their teens and they're now using a wheelchair, and they have mixed spasticity and dystonia and triplegia. This person very likely does not have CP. They didn't have any motor difficulties until they were in their teens, and it looks like they've been losing function since then. These are red flags that this person actually does not have CP. I point this out because there are many adults that we see in our practices that carry CP diagnoses who may or may not have CP, and it's important to be vigilant to avoid anchoring that comes along with seeing a diagnosis in someone's record and making sure that someone does in fact have the diagnosis they came in with. This is a classic example of not CP. Lastly, there's a 25-year-old person with CTNNB1 pathogenic variant. This is a very common variant that we see in genetic studies associated with spastic diplegia. They have motor delays without regression. This person also has CP, barring anything else in the history that might suggest otherwise. This surprises some people who might think that CP is due to exclusively an acquired brain injury and cannot be due to genetic findings. You're going to be hearing more about this later today, specifically with regards to the AAP genetic guidelines that have been recently released. But I wanted to point out in particular for CP, the genetic etiologies really do matter. CP is a clinical or phenotypic diagnosis. It's not etiologic. In that way, it's a lot like autism, which we just heard about. You can have a genetic etiology for autism. You can have autism in a child who was born preterm as the main cause of their autism. So you can still have CP and have a genetic etiology. In fact, estimates ranged up to 30% of people with CP potentially having genetic etiologies. This includes importantly, people with other risk factors for CP like prematurity. For this reason, there's been a lot of interest in thinking through genetic testing in people with CP, and this work that was led by Sid Srivastava, which we collaborated on shows that an exome study is likely the highest yield to study for detecting a genetic etiology of CP. The ACMG also recommends whole exome or whole genome testing first line for developmental disability, including CP, and that's because it changes acute or long-term management in up to 8-10% of people. That is independent of family planning or prognostication. That includes things like screening for coexisting conditions that might be life limiting like cardiac or renal conditions. Because of that, we've just now advanced an American Academy of Neurology quality measure saying that genetic testing should be a part of clinical discussions with families that are affected by global developmental delay, intellectual disability, epilepsy, or cerebral palsy. I point this out specifically for CP because in our practice, every single person with CP, we are now sending for whole exome or whole genome sequencing. You'll be hearing more about this again when you hear more about the AAP guidelines later today, but I wanted to make sure that for CP, you all knew that this is now becoming standard of care. Now that we know what CP is and the genetic part of that initial evaluation, how do we think through tone management? Step 1 is goal-driven care. Many of you may already be familiar with the WHO International Classification of Functioning, Disability, and Health. I'm a child neurologist. The way I was trained, and I think the way most clinicians are trained, at least most physicians are trained, you think about the health condition and body functions and structure, and you tend to not necessarily at the outset, think about the other factors that affect someone's functioning and participation in their community. In this case, I might evaluate someone with spastic hemiplegic cerebral palsy. I'll notice that they have certain findings on their exam. Based on those findings and their condition, I'll say, let me treat these findings, put in a blanket referral to PT and OT and think about Botox. That could be fine and will get you to a certain place in that person's care. But digging into the things that are really important to them matters and should guide how we think about tone management in an evidence-based way. You learn that one of the main things this child is interested in doing better is in gripping things. When you figure out, you ask why, and it's because they're having trouble with cutting and crafts at the end of the day at school. You also hear that

they're falling a lot more at the end of the day at school. You notice that there are features about their home that are inaccessible that are contributing to fatigue. You also learn in environmental factors that their IEP was discontinued because this person passed school-based assessments for participation, which don't necessarily take into account fatigability towards the end of the day. You also learned that there are several personal factors that contribute to stress on the family and ability to access therapies that this child might need. I'm not going to go into detail here, we all know that each of these things trigger other needs for this child that may actually be far more beneficial than Botox, than botulinum toxin. Thinking about what that child needs separate from your tone exam in the clinic, is critical for making sure that we're optimizing that child's function and their participation in society. Lastly, I want to point out that particularly in people with disabilities, but really for everybody overall, it's very important to document that person's baseline. That's because I mentioned anchoring already, there is a tendency or there could be a tendency to say that anybody's decline in function is just their "CP". Making sure that we're documenting someone's impairments and someone's functional abilities across domains can be really critical to communicating to other clinical providers about what this person's functional abilities are now and that a deviation from that should trigger further workup. In that sense for CP, the classic, what's been called a CP vital sign is documentation of gross motor function using something called the gross motor function classification system or GMFCS. The GMFCS is split up into five levels. These levels characterize how someone gets around in the world, include things like independent ambulation without an assistive device, independent ambulation with an assistive device, and that's getting to Level III. At Level IV and V, this person is using a wheelchair primarily to get around and explore their world. A critical reason to document GMFCS beyond establishing someone's baseline is that, at least in childhood, the GMFCS level should stay stable. Beginning at around Age 5, you shouldn't really be jumping between levels. If you do see a person with a change in their GMFCS level that is associated with increased impairments or loss of function, that is an urgent evaluation need that might necessitate tone management. It should also probably necessitate why this person with CP is losing function. Establishing someone's GMFCS level is a very hard way to say, this is the functioning that this person is currently achieving, and it really should not deviate from that. If it does, that is an urgent medical need that requires evaluation. We talk a lot about walking when we talk about people with motor disability, cerebral palsy in particular, I just call GMFCS a vital sign for CP. GMFCS is not the only way, gross motor function is not the only modality of function. There are other functional classification systems for CP for manual ability, communication, eating and drinking, vision. I want to highlight in particular under communication, the CFCS that communication is verbal and nonverbal. There's a separate scale to assess or describe how someone verbally communicates. But there are people that have excellent communication that don't do so verbally. We do our best to document both the CFCS and the VSS. This is a lot to document. We've incorporated this into our workflow using a lot of standardized documentation. For those of you who are interested in learning about how to document these levels, again, I have a QR code at the top of the screen that you can use to access how to classify GMFCS levels across age, and how to classify each of the other systems and scales that I have mentioned across levels for people with cerebral palsy. One more pit stop before I get to tone management, and that's thinking through other general features of mobility optimization that should and can be done independent of tone. This includes orthotics. I want to highlight two particular orthotics. One is a trunk support vest, a Benik vest. I think we think a lot about high-tone management, spasticity and dystonia in particular. A lot of people with cerebral palsy have significant low tone, axial low tone, and axial weakness. A trunk support vest or a Benik vest can be incredibly helpful for that. I also want to highlight the value of a stretching splint and how that can be useful to increase range of motion, particularly in combination with botulinum toxin injections. I'm happy to talk about other orthotic management as people see fit. Durable medical equipment, DME is really critical for optimizing mobility in people with CP. Something that we are really stressing, particularly in our young children with CP is something I used to call early mobility, but it's really should be called on-time mobility. If you expect a 12-18 month old who's typically developing to be able to pull to stand and start taking

steps and start exploring their world, and someone has motor impairments at that age that are preventing them from doing that, then they should be getting prescriptions for DME to allow them to engage in on-time mobility and explore their world that is not dependent or such that they are not restricted by their motor impairments. We also think about other seating interventions like wheelchairs, strollers, bath and activity chairs. As people get older, we think about lifts for the home. Standing is incredibly important for hip development, bone development, and also for reducing GI symptoms like constipation. We really monitor whether people have a standard at home and at school and how often they are able to stand, including writing notes for IEPs to make sure that standing is time is being optimized at school. We advise at least 10 hours a week. We also make sure that people have access to communication devices if they have limited verbal ability to communicate. We also make this referral sometime 12-18 months of age because that's when on-time communication is just as important as on-time mobility. We make sure that our children have access to all of these things as would be expected in the typical developmental timeline. We've talked about goal driven care, optimizing function participation. Now let's talk about spasticity and dystonia and tone management. When we talk about dystonia spasticity in people with CP, we often think through different types of hypertonia. Rigidity is one type of hypertonia that's associated with constant resistance, regardless of velocity of passive stretch. It's incredibly rare in children. If you see that someone is tight and they are constantly resisting, regardless of how fast you're stretching their arm, that is a red flag that should actually prompt immediate evaluation for other conditions that might be neurodegenerative or treatable, like neurotransmitter disorders. Be on the lookout for that very rare form of tone. Spasticity is a very common form of tone in people with CP, that is increasing resistance to increasing speed of passive stretch. Stretching someone very fast will trigger a catch, but stretching someone slow, you might feel less resistance to that stretch. Spasticity is present all the time to some degree. Yes, maybe there's a little bit of fluctuation in how much spasticity someone has, but if someone is tight in a certain muscle group, they're always going to be tighten in that muscle group, whether they're awake, sleeping, sick, healthy, whatever. Spasticity is also not triggered by voluntary movement, typically. Dystonia, on the other hand, is classically triggered by voluntary movement. Every time you try to move, a part of your body that you do not want to move moves out of your control. It's also arousal dependent, so heightened emotion like stress or anxiety in particular can trigger dystonia. Dystonia is classically variable. It is almost always gone in a child who's asleep. In addition to that triggering factor, which is in contrast, spasticity, it can not be there in muscles at some point and can be there in muscles at other points. These types of tone can look very similar in a snapshot, but are very different in terms of how they present in the same person over time. When we think about how to differentiate spasticity and dystonia, this is the SCPE classification system for CP, thinking about whether someone has spastic CP or dystonic or dyskinetic CP, they go through, is the tone persisting, or is the tone varying? Then they say, "Well, if the tones persistent, you have spasticity, predominant CP, and if the tones varying, you have dyskinetic of which most people have dystonic predominant CP." The breakdown here is 85% spastic versus 15% dystonic, and that's where we have lived, thinking about spasticity and dystonia some time. But in real practice, we know that there's significant overlap. When we characterize our own cohort at St. Louis Children's, we know that about 70% of our population has spasticity predominant CP, 17% has dystonia predominant, but over half have both in the same person, and that's common that the majority of people have both spasticity and dystonia. Differentiating between them is critically important. It can be hard to do that on exam. It can be hard for any of us. It's hard for me to do that on exam, and I'm a pediatric movement disorders physician who's dedicated her life to this. I rely a lot on the expertise of caregivers and people with CP to help me differentiate because when I'm in clinic, I'm seeing someone for 20-30 minutes while there are other kids are running around. I'm trying to get prescriptions written. It's a lot to be able to sit and observe someone in peace in the short periods of time that we have. We ask caregivers and we ask people with CP, when you try to move one part of your body, do you move another part without meaning to? Or during activities where someone handles you, do you move a different part of your body without meaning to? Or, namely, an easy one, if you right now your child feels really tight to me.

Are they always this tight? These sorts of questions can help you dive into whether or not that tone is variable or that tone is constant, which can give you a guide as to whether this tone is dystonia or spasticity. When we ask family this with no other instruction, this was a survey that we handed out to families, a one page survey. If they said yes to both questions, that had a 92% positive predictive value for dystonia. If they said no, that had a 77% negative predictive value for dystonia. If nothing else, asking families these two questions can give you a pretty good clue as to whether dystonia is something you need to worry about. When thinking about dystonia, There are a lot of tone management options. The only chance you have to treat someone's dystonia is to manage its triggers. If you have not managed the triggers of dystonia, you have no chance of getting rid of the dystonia itself. The most common triggers in CP are pain, poor sleep, and heightened mood, typically negative emotions like anxiety or stress. If we again look at our center, at least 25% of our kids and young adults are affected by one of these triggers. There are different ways that we approach treating these triggers specifically to reduce dystonia. Now, I want to highlight the heightened mood aspect in particular. For whatever reason, a lot of people in the community and a lot of people in medical practice, to be honest, carry a lot of stigma in treating mental health conditions. I often couch putting a child on an SNRI like escitalopram or fluoxetine, for example. I couch it as saying it's a treatment for their dystonia, because I need to reduce the anxiety trigger for your child's dystonia in order for their tone to get better. That is often, for whatever reason, much better received than saying, I'm treating your anxiety with this SNRI, or I'm treating your mood mobility with this antipsychotic, and both are true, but often people are coming in for the tone, and we have to dig in and understand what the mental health triggers are, and help address those to have any chance of reducing the tone itself. I just wanted to share that clinical practice with you all. The pharmacologic data, and this is a talk on evidence based tone management. We don't have a lot of evidence for how to treat dystonia in particular, or spasticity, for that matter, in people with CP. This is a beautiful meta analysis done by Darcy Fehlings and colleagues. I'm showing you this table of enteral medications to treat dystonia, namely to show you that the only medications of all of these assessed that we have any data on are these three trihexyphenidyl, clonidine, and levodopa. The only medication of these three that showed any improvement in dystonia in people with CP was clonidine, not trihexyphenidyl, not levodopa, which for any neurologist in the audience, these are classically our Number 1 and two go-to treat dystonia in young people. But it's at a population level, they showed no benefit, and it was only clonidine that has any evidence to support its use. Are we actually following that in clinical practice? When we surveyed physician experts that based on memberships to national societies across the US and Canada, the majority were using baclofen first line to treat tone in people with CP, which makes a lot of sense. As I mentioned before, because spasticity and dystonia often coexist in people with CP and baclofen can also be used to treat high tone, regardless of whether it's spasticity or dystonia. Then you see the rest of the medications here. Trihexyphenidyl, carbidopa are up there, but clonidine is not. Something I would encourage you all to do in your practice is not forget about clonidine as a tone medication for CP, particularly for dystonia. It is in fact the only medication that has any evidence supporting its use. I include this table. Apologies. It is busy. I hate being the person that says that, but I'm including it because I think it is a good reference for dosing guides, indications, and contraindications for each of these medications based on the clinical practice of physician experts in CP. I'm also highlighting that baclofen and benzodiazepines, this is all data supporting treatment for dystonia, but baclofen and the benzodiazepines are also commonly used for spasticity, which again is why baclofen is typically the first line medication we use for pharmacologic tone management and cerebral palsy. Based on the limited data, there is an expert consensus based guideline that we worked on through the American Academy of Cerebral Palsy and Developmental Medicine that was against spearheaded by Darcy Fehlings. They note that first line, Diclofenac, they suggest against the routine use of Tyonex, benzodiazepines, and levodopa. What I would say is that in my clinical practice, I do not use these medications first line, and I typically turn to them third or fourth line. After baclofen, my second line medications are, as indicated here, clonidine or gabapentin. I already gave you the dosing that is typically used for gabapentin on the previous slide, and here's the typical

dosing for clonidine that we use to treat dystonia. Moving on from enteral medications. These are the injectable and surgical treatment options for dystonia. All of these actually have data supporting that they're beneficial for reducing dystonia in people with CP. To break that down a little bit, the injectables, we think about botulinum toxin and phenol or ethanol injections. Botulinum toxin, there's been a paradigm shift in recent years. We used to have people that had been getting Botox for their whole lives. Started when they were kids, now they're 45, they're still getting Botox to a wide range of muscle groups. We colloquially call it a Botox dip. People that are getting Botox to legs, arms, neck. We've all seen people that have been getting this for years. There is growing concern that long term use of Botox may actually cause long term weakening of muscles, which, though the data for this is soft and largely pre clinical, does in fact make intuitive sense. What we're trying to do now is move towards botulinum toxin as a goal targeted intervention for a few years, noting that we're pairing that with intensive therapies, stretching splints, and focus on range of motion, and noting that if someone is not able to increase or optimize the range of motion with botulinum toxin, we're often next up thinking about orthopedic surgical interventions. I tend to think about botulinum toxin as predominantly useful for spasticity over dystonia because it is a muscle weakener, and in someone with dystonia is their predominant form of that tone. Oftentimes when the dystonia is not there, that arm is quite weak and hypotonic. It's difficult to add Botox, which is a continuous effect medication as a primary treatment for a pure dystonic limb. But for mixed spasticity and dystonia, it's a great choice. Phenol and ethanol injections typically used to decrease spasticity in leg adductors. This is often painful or typically painful, so we typically do this under anesthesia. Surgical options, I want to talk about orthopedic surgical options first. These are often used to treat musculoskeletal results of hypertonia, namely contractures and bony deformities. There is a misconception that dystonia cannot cause contractures. Trust me, it does in people with cerebral palsy, depending on the severity and tonicity, how longstanding someone's dystonia is. But it's also important to note that in someone with variable tone, if you're changing someone's muscle and joint dynamics in a fixed way with an orthopedic surgery. Dystonia is dynamic and variable. Dystonia can be a real confounder and limit the efficacy of orthopedic surgeries. It's important to identify where dystonia is contributing to joint dysfunction and where spasticity is contributing to joint dysfunction before moving forward with an orthopedic intervention. We use collaborate with our orthopedic surgeon colleagues a lot for soft tissue interventions like tendon lengthening to increase range of motion and help address spasticity. Combined tendon lengthening across multiple levels with bony interventions can be called a SEMLS or a single event multi level surgery. Then hip reconstruction is often necessary in people with CP at GMFCS levels four and five, three, four and five, in particular, who have significant leg adductor spasticity, which can limit hip growth. That hip dysplasia often leads to hip reconstructive surgeries as well. Surgical options for tone management. This can include intrathecal baclofen, which is typically for spasticity management, typically in the lower spine, it tends to be targeted to the legs. For dystonia, intrathecal baclofen management is in the high spine with the idea that that baclofen may actually be infusing into the brain as the primary source of efficacy. Although we say you can do ITB for both, it's a different locations often for spasticity versus dystonia. Deep brain stimulation is available at select centers. It is for dystonia only. It is generally thought to work best for hyperkinetic dystonia, meaning that someone is constantly moving because of their dystonia. There's a very specific population for this, again, available at select centers. But if a person you're seeing is refractory to medication management for their dystonia, this is a great option. Then selective dorsal rhizotomy is a spasticity only surgical option. In this process, you have a reflex arc, that governs driving of increased tone. You have reduced drive from the cortex. You have a reflex arc from the spine through sensory nerves back to the spine. Selective dorsal rhizotomy cuts some of the sensory arc, and it is exclusively for reducing spasticity. There are variable reports of it actually worsening dystonia. Making sure that you've identified how much spasticity is contributing to someone's goals and not dystonia is critical. The age and GMFCS level, typically at younger ages, typically at GMFCS levels 1-3, but we see it at higher levels 4 and five as well. Requires good leg strength and selective motor control. The last surgical intervention I want to talk about is ventral dorsal rhizotomy. This is a

newer procedure where or in addition to or instead of cutting the dorsal roots, you can also cut the ventral roots, and this causes weakness by design and is sometimes called a palliative rhizotomy. This is beneficial for treating mixed spasticity and dystonia and is particularly useful in children who are not bearing weight or do not need to bear weight anymore as part of their goals to facilitate hygiene and positioning, particularly in the legs. I know I'm over time. I'm going to take just one or 2 minutes to close and take you through a flow sheet guiding you through tone management, at least how we perceive it in the St. Louis Children's Hospital CP and mobility Center. Everybody should get what is in this box goal centered care, orthotics, DME, on time mobility, therapies, range of motion based interventions via those therapies. That's for everybody with CP and motor impairments. Based on whether they have low axial tone or decent axial tone, meaning, can they tolerate a whole body tone med that makes them reduces their tone full body or not, Baclofen is first line. Or if baclofen is not enough or they have poor axial tone, then you really have to start differentiating between spasticity and dystonia. For spasticity, we're thinking about ejectables, tendon releases. Really, if you needed benzodiazepines, but we try to avoid them for their sedative and cognitive depressing properties. Dystonia, we have the meds that we use for pain trigger dystonia, gabapenin sleep triggered dystonia, clonidine, and mood trigger dystonia, with Txpnadol and levodopa being sort of the last line options. The next stage surgical options are indicated here, SDR, ITB for spasticity, DBS and ITB also for dystonia. There are some centers that are starting to do lesional treatments for dystonia as well, and this is very new, and so I haven't talked about it, but I'm happy to discuss if there are questions. Then lastly, if these surgical interventions still don't feel like enough, the ventral dorsal rhizotomy or palliative rhizotomy, as it is colloquially called is an option. This is highly center dependent. I want to highlight that our center doesn't offer some of these treatments. It only offers some of these treatments and not all of them. Make sure that you're reaching out to centers. I guess what I'm saying is don't feel bad if your center doesn't offer all of these. There are centers that must work together in tandem to offer surgical treatments at a high degree of expertise.

Dr. John I. Takayama: One question that comes up has to do with sort of the genetic component. I guess two questions and one. Do the long term outcomes vary based on brain injury versus genetic component? I guess, can you have a CP diagnosis secondary to genetic ideology with a normal MRI?

Dr. Bhooma R. Aravamuthan: Yes. Let me I'll answer the second question first. I might have you repeat the first question. Can you have CP with a genetic diagnosis in the setting of a normal MRI? Yes. In our clinic, about 12% of our kids with CP diagnoses have normal MRIs. And often if you have a normal MRI and CP, a genetic etiology is high on the differential for for why you might have CP. I'm sorry, what was can you repeat that first question again?

Dr. John I. Takayama: Do the long term outcomes vary based on.

Dr. Bhooma R. Aravamuthan: Oh, yes.

Dr. John I. Takayama: Whether it's brain injury or genetic?

Dr. Bhooma R. Aravamuthan: Great question. It turns out so we don't have the hard data for long term outcomes for many genetic conditions because we're only starting to recently identify them, but we do know for infantile onset HSP, which is often diagnosed as CP or has been diagnosed as CP before people had access to genetic testing, their long term prognosis is comparable to the long term prognosis of people with CP, and many people would think that HSP, hereditary spastic paraplegia, always has to be diagnosed as HSP and not CP. That is not true. If someone clinically meets criteria for CP, feel very comfortable giving them a CP diagnosis, the prognostic data is based on that phenotypic diagnosis, and for sure, up to 30% of that population, whether it was set in those initial prognostication studies or not, had a genetic contributor. The prognoses are comparable.

Dr. John I. Takayama: Thank you. But it sounds like there's some similarities in prognosis then. You

raised the issue of fatigue. I'm wondering if whether it's school or whether it's the therapy, whether that needs to be modified to consider the fatigue. If it happens more in the afternoon, should it occur more in the morning or, should the curriculum vary based on that or more in rests?

Dr. Bhooma R. Aravamuthan: This is this is a great point. We in particular, for us, where this comes up is in our kids with spastic hemiplegia, which is why we used and published on this example. Because at the beginning of the day, it may seem that this person is functioning incredibly well and doesn't need any supports, but it's over the course of the day that the supports are really necessary. We work very closely with families and schools to think through the IEP and think through supports for this population, including things like having access to wheelchairs and walkers between classes at the end of the day or making sure there is someone available towards the end of the day to help support the person. For some people, we have had their periods, their class periods switched. The more activity intensive classes occur at the beginning of the day than at the end of the day. This requires a really collaborative approach and an understanding that people are different, their needs are different. We work through all of those things that you mentioned for our families.

Dr. John I. Takayama: Thank you very much. It's a dynamic setting and you really have to provide student or patient centered care.

Dr. Bhooma R. Aravamuthan: Absolutely.

Dr. John I. Takayama: Okay. Great. Because of time, I'm wondering if you might be able to answer offline the Q&A. In the meantime, we're going to go to the next speaker.

Dr. Bhooma R. Aravamuthan: Absolutely.

Dr. John I. Takayama: Thank you so much.

Dr. Bhooma R. Aravamuthan: Thank you.