Ask the Doctor Session – Pediatric Issues

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00:00:00 [Beginning of Recorded Material]

Dr: Vellody: Thank you guys for coming out on a Sunday morning! I know that's a challenge sometimes and I know that sometimes people are late. But feel free to text your questions or write them down or ask them if you feel comfortable. I am the Medical Director of the Down Syndrome Center in Pittsburgh. It is one of the oldest centers in the country - I think it was created in 1989 or something like that. And it was created by parents who, just like you guys, had questions about DS but realized that it's really hard to find answers from somebody who is not familiar with Down Syndrome. So they created this center to take care of the medical, developmental, behavioral aspects for the kids, and over the last 27 years now, the parents' group continues to be the major contributor of all that we do.

Here, we have Sheila Cannon who is our program coordinator of our center. She has a Master's in Education and a developmental background as well - so she helps with that side of things. We have an adult physician, Dr. Bullova, who takes over from 18 on. And now, over the last couple of years, we now have a transition specialist - someone who works on teenagers to help them transition into the adult stage of life. We also have a nurse, a part time nurse, so it has really, really grown. We have just added another adult physician because, as you might imagine, adult providers are even less comfortable with what's expected, what's not expected for adults with Down Syndrome. So it's really been a need in our community and we're one of only about 8 centers who do the whole life-span, type of approach to care.

Any questions that you ask we'll be answering in a more general type of a way and we'll probably be expanding on some of the topics as well to address other questions that I've heard over the years and answer those as well.

We both, Sheila and I, have family members with Down Syndrome. My brother has Down Syndrome and this is why it's my favorite tag! So we both have a passion for this and that's why we're here.

The first question is about a two year old who has had multiple scans that have not showed any of the brain structures that we typically see in many people with Down Syndrome. I guess my first question is why are they doing all those scans? That's a lot. We don't typically recommend the whole CT scan to the whole body - that's a lot of radiation, a lot of exposure; we do know that over-exposure from

radiation and CT scans can definitely be harmful to people. I would really ask if there's an actual role to doing all of those scans, and then to specifically answer your question: certainly for many people with Down Syndrome, the anatomical structure, the look of the brain, can be different than a typically-developing child. The cerebellum which is where we get our balance from tends to be smaller, and some of the other areas of the brain can also have a different appearance. This can mostly be seen by MRI scans - certainly CT scans can't give us a lot of detail of those structures in that area. So I don't know necessarily if it would mean anything one way or another in terms of what that would mean developmentally. I think, what I always get asked about is 'where my child is going developmentally?' If I had my crystal ball, I'd be making lots and lots of money! But I don't - and therefore, all we can do to predict development is just watching them at each stage. And that is why at our center, we see the babies usually around 1 to 2 months old sometimes even in the nursery. And then I see them at around 1 or 2 months of age as well. After that, we follow them every 6 months to see what track they are headed on - seeing if there is anything extra that we can do, any extra support that we can give. For example, as you might now, Early Development Services, though they are federally mandated to be available, are not federally mandated to be good. And because of that, a lot of the times we try to figure out if that child is going to need extra support, gross motor skills, fine motor skills, and helping them out in any and all areas necessary.

Going back to the original question though, I don't know if those scans will really change much in terms of how to approach your grandchild and what to expect from them. And I would really caution you just from the radiation and pediatric standpoint. But again, just to reiterate, what something might look like in picture-form on a scan, doesn't mean that it's going to correlate with development. Lots of parents come in saying, "Well my child doesn't have those abnormal structures, the wide gap between the toes; does that mean my child is going to be better developmentally?" And the answer to that is just no. It doesn't. It's all about just following the child throughout each stage of development and seeing where it goes from there.

The next question is about leukemia and when do we get most concerned about it and when can we sort of alleviate that concern.

If there is one thing that I wish I could just take out of the list of things that are higher chances in people with Down Syndrome, it would be the leukemia. It's the one that so many families lose sleep over because it's so scary. I guess that there's a couple of things we should say about the whole thing before getting into specifics. The risk of leukemia - the chances of getting it in someone with Down Syndrome - is quoted at around 1%. That means that around 99% of people with Down Syndrome will never have leukemia. And while you would never want to be that 1%, it can still be reassuring to know that it is indeed a very small percentage. The reason why we even talk about in DS is because, in kids without

DS, the risk for developing leukemia is around .1% so there's about a 10x greater chance of developing in our kids. But still, it's very low chance.

Then, when we look at the typical age ranges of when we'll see it, some kids are even born with symptoms like leukemia like we talked about in the medical conference yesterday. We were talking about Transient Myeloproliferative Disease - TMD - and this is where a baby right out the womb is actually born with leukemia. And this happens in about 10% of newborns. But the strange thing about it is that, although to everyone, on all the blood smears, it looks like leukemia - which it is - it actually goes away completely on its own in about 3 to 6 months. However, those kids are now at a higher risk of getting actual leukemia at some point - their chances now go up to 30%, instead of 1%. That's why it's really important and part of our guidelines to check the blood count of every baby with Down Syndrome at some point in the first week or so of life. That way, we can identify the kids that are, unfortunately, at a higher risk of leukemia.

The second part of it is, what is that age range? Typically we say, usually in those first 5 years of life is when the kids are most susceptible for it. But when you look at the type of leukemia that people with Down Syndrome get, it's a very specific type called AML - Acute Myeloid Leukemia. It's a very specific type of AML that is actually better treated than it would be in a child without Down Syndrome. It's a very interesting phenomenon, well you'd think it's common sense, but when doctors share information about best practices on how to treat something, you find better ways at treating specifically specific groups of people. The Children's Oncology Group - which is a nationwide combination of pediatric and oncology specialists who deal with leukemia -- they share their protocols. It just goes thought the system. And then what happens over time is, they modify different parts of it, and then you find what thing works best for boys who have Down's Syndrome, who have AML; and in this way, you get very, very specific and then next thing you know, you find things that people with Down Syndrome respond really well with chemotherapy and who are then able to go into remission at a much higher rate than kids without Down Syndrome who get AML.

As a father, would I ever want my child to get any type of leukemia? No. But if we make a diagnosis of leukemia within our clinic population, it doesn't have the same feeling of no hope. It's actually the opposite. Yes, of course, it's a very rough road to go through with chemotherapy and everything but the outcomes are so much better for people with Down Syndrome than for people without. Does that kind of make sense? I mean, I'm not trying to lighten the burden that any family has when having a child with leukemia at all, but it is much better to go through that struggle with a positive outcome than the other options.

So then the next question is about do you actually have to do routine blood count on people with Down Syndrome which was from my slides during the Medical Talk yesterday.

The only time you actually have to have a full screening is during the first week of life. This is to check for that Transient Myeloproliferative Disease. But the problem with the idea of screening - I wish we could - is that it's not like if you check a blood count today, you're good for a year. It's not like thyroid where your kids go get their thyroid checked and they're good for the next six to twelve months depending on their age. It's just not like that with leukemia. In fact, there's at least two children that I'm thinking about where we saw them in clinic on let's say a Friday, we did a blood count - because part of our guidelines is to look for anemia in kids because iron deficiency is common - and then on a Tuesday they're in the ER with a fever, nose bleeds, bruising, and sure enough they have leukemia.

And so, there's no screening for it, and I say that not to scare anyone but basically, if a child was to have leukemia - which again, is so rare - it's not subtle. It's very obvious, it's a huge change that families notice with the high fevers or the loss of energy, nose bleeds, bruising, that kind of thing. Again, it's very rare. This year we saw about 500 patient encounters in our pediatric clinic. And I don't think this year we've actually had any new diagnoses so it's a very rare thing to see. But of course, you get nervous about it - totally understandable.

00:14:43 The next question was, "What are the regular specialists that somebody with Down Syndrome should be seeing and how do you know?"

That's a great question and really, that is more individualized in terms of if there's a problem that requires some specialist that we'll refer to. A lot of the times there are ear infections and sinus infections and this of that nature that requires a specialist like an Ear Nose and Throat Doctor would be good. Those kinds of things. For sure, according to the guidelines, everybody by the age of six months should be connected in with an ophthalmologist - an eye doctor - because eye issues are very common in people with Down Syndrome and what regular doctors may see may not be anything like what the ophthalmologist would see with their special toys and gadgets. And so, ophthalmology, we start about around six months of age and usually go annually for the first few years of life. Then audiology - which all babies in this country get in the newborn period, gets repeated again at around every six months for people with Down Syndrome, and the reason for that is that hearing loss is so common and develops really in almost 1 out of every 2 people with Down Syndrome – they'll develop Transient Hearing Loss at some point in their life. The reason for that is that the liquid in the middle ear just doesn't drain out as effectively in people with Down Syndrome as it does in others. And so, the fluid just gets stuck in there and then it can either get infected or it just gets stuck there and impacts the hearing. After that, the kids can't develop their speech – hearing impaired kids can't always learn how to speak. Lots of parents will say, "Oh! He always hears me from the other room!" Well you don't know. Is he hearing the specific sound patterns that he needs to hear to make speech, or is it muffled like that and he's just responding to the

sound versus the actual speech. So that – ophthomology, audiology – those are your specialists for sure, for everybody, that we start in the newborn period.

00:17:25 So really, the question is, in terms of the role of a Down Syndrome special center. That role is really to supplement what the pediatrician is already doing. Because you can imagine what a pediatrician is doing, seeing 3,000, 4,000 kids a year, and so by statistics alone, maybe 3 or 4 of those kids will have Down Syndrome. A general pediatrician of family practitioner, therefore, really doesn't have time to memorize 16 pages of AAP guidelines on every single kid that comes in – it becomes hard to know when to refer to this or who to refer to for this – and that's a big part of what we do. There are certain sub-specialists that are really good at working with our patient population. And then there are others where I wonder if they've ever seen a child before! It's really important for us, we kind of establish a pattern with the specialist and then that specialist, for example an ENT, will know all those ENT issues in Down Syndrome because I'm sending them all the kids. Then, they get really, really good at knowing "okay, I need tubes for this one, but you know, with this one, I think I can wait." You get comfortable with your referral pattern for the specific type of patients that you see – hard to do that if you're a general pediatrician in the community.

00:18:48 The other thing to empower parents too that's really important is the health care guidelines are availbable for free for anybody. You can get the medical version, if you want it, and send it to your pediatrician so they can keep a checklist in their office in terms of what needs to be done at what ages – it's broken down by age. There's also a parent version as well. The medical version you can find on this website: www.pediatrics.org – those are the medical guidelines. And the other one for parents is at www.healthykids.org – which is also really helpful. For our specific clinic, of course, you don't have to bring that in because we have our own checklist that we've made from these guidelines. But for the families that are going back to their pediatricians, we will actually send them the guidelines from our centers – that's one of our roles. And then the families, we ask them to also bring a copy of the guidelines any time they go to their pediatrician. Especially if they're not following up with us regularly – the distance might be too much of a hassle, whatever, they should know the guidelines.

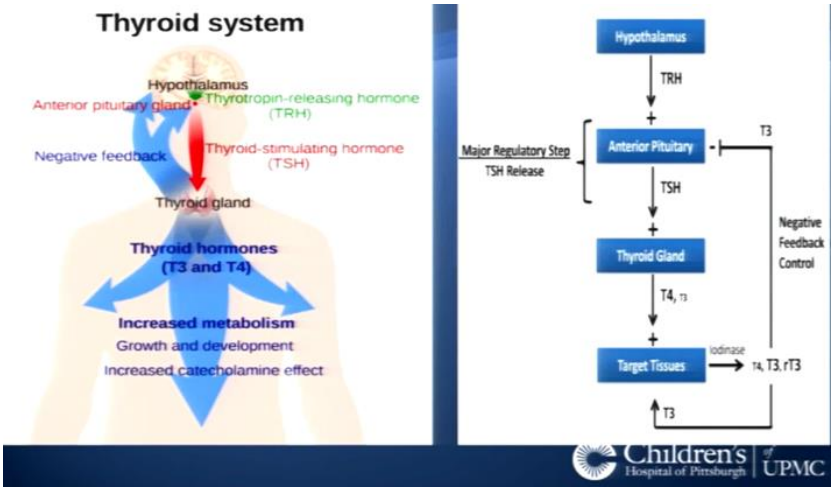
Audience: [Question, unintelligible]

Ms. Cannon: Every state is so different. In Pennsylvania, all of our children qualify for medical assistance as a secondary insurance. So it's typically not a problem in Pennsylvania – you can go wherever you'd like to go – but I don't if Florida has that type of program there because it's not related to income; it's related to disability in Pennsylvania. The other thing that I was going to recommend: care coordination is becoming quite the trend for insurance companies because they can streamline the progression of care much better and so I'd definitely

recommend calling your insurance company and talking to them about what your child's needs are.

Dr. Vellody: There's about – in terms of active Down Syndrome Clinics in the country – 40 to 45. When I say "active", when you look at the list there's probably more than that, but some are more developmental clinics that just happen to see kids with Down Syndrome, and some are clinics – like us – which this is all we do. We only look at kids with Down Syndrome. If you're looking for a list of Down Syndrome Clinics, you can find it on the NDSC website and there's a list there. We're actually in the process of forming a test to update the list and make sure that we call each and every one of those clinics and asking them, "What exactly do you do?" so that list is as accurate as possible. Compiling a list is one thing; having an accurate list is more important.

00:22:25 The question is about thyroid levels, when to treat, when to watch. And it's a great question and I think it's one that is probably more common than you might realize. This slide I use in the Medical Talk that I gave yesterday.



I know it seems busy when you first look at it but the left picture just shows where these glands are that make the combination of TSH and T4 and them. On the right, it shows you a more diagrammatic way of what is going on. Thyroid is actually a very complicated thing. The first thing that is created is in the hypothalamus is TRH - Thyrotropin-releasing hormone. That goes a very short distance to the pituitary gland where the TSH is then formed. The TSH is formed and then travels through the body and goes to the thyroid gland which sits in your neck and that's where T4 comes from. The two numbers that when we're trying to interpret thyroid function is the TSH and the T4. TRH – it's pretty rare to have a problem with that hormone and so it's not common enough to test, certainly not more common in people with Down Syndrome.

When we look at the way that this works, the red arrow in the slide shows the travelling between the pituitary and they thyroid gland because the TSH is what

tells the thyroid gland to make more thyroid hormone. The thyroid glands then make more T3 and T4 and that T4 is what actually then goes to the body and tells it to go do the things it needs to do. Things to do with metabolism, and growth, those types of things. The important thing is asking, 'are your target tissues receiving enoughT4? Are they getting enough of that thyroid hormone to do what they need to do? Because if the T4 starts to drop, your body's natural response will be to kick up the production of TSH.

Now the normal range of TSH changes by age but a good idea to look at it by is around .8 to 5.5 or 6. That's a good range for TSH. As it starts to creep upward, that's a sign that your body needs to give more effort to produce more of the T4 – your body starts to sense that the thyroid gland is getting tired and not working the way that it should.

What happens sometimes is there can be a transient thing. Let's say, you get sick with a cold. And when you get sick, your body actually needs more thyroid hormone and so your TSH levels will naturally rise in times of illness. Because of this, if we happen to catch a child during a time of illness, we're going to get a transient elevation of the TSH. But even that, we never expect it to go into the double digits. Now once we start getting 10 and higher, that's when we can start getting concerned about possibly hypothyroidism as something that could be more common in this child. Most of us, if not all of us, who take care of kids with Down Syndrome, use our cut-off as 10. If the TSH is consistently above 10, then we usually start thyroid medication. It's just that, as you all I'm sure know, everything in medicine is a risk/benefit type of thing but the benefits of treatment are far better than the risks if your TSH is starting to creep up like that.

00:27:10 When the TSH is, let's say, in that 6-10 range, that's a real question mark. Because, could you be having that transient elevation that we were just talking about, or are you 7 today and are going to be 15 in three months – that'd be a whole different story. And so what we do in that mid-range thing, we repeat the thyroid hormones check usually in about 2 or 3 months. And along with that repeat, we'll also send thyroid antibodies. These thyroid antibodies are actually produced more frequently in people with Down Syndrome – we don't exactly know why that is – but people with Down Syndrome just are able to produce more antibodies, and some of these are actually against themselves. Normally, we make antibodies against the flu virus but in people with Down Syndrome, they'll make antibodies against certain parts of their own self. And so, one thing that you'll hear – autoimmune thyroiditis or Hashimoto thyroiditis – those types of terms, those are just saying that there are antibodies in the person's blood stream that are essentially destroying the thyroid gland making it less able to make the T4 that it needs to make.

As that TSH starts to rise and there are the thyroid antibodies present and TSH and the TSH is getting above 10, then we typically start to think that child is

getting to, if not already there, hypothyroidism. After that, we'll start the Synthroid then.

00:28:53 Follow up question: "What are the risks of being on Synthroid."

Synthroid, which is another way of saying Levothyroxine, which is another way of saying T4, is a synthetically made thyroid hormone. Essentially, if you have a hypothyroid and are not making enough T4, then what the Synthroid does, it replaces what your body can't make. It helps because it's essentially not a medication in the sense of where you're giving something to somebody for their cholesterol and now there are all these side effects, it's not like that. For Synthroid, you're just replacing what your body should naturally be making. The main issue that we run into, and some of you might be aware of this from the Internet, is that some of these "experts" on the Internet will say that every person with Down Syndrome needs to be on Synthroid and that you can't trust the normal lab ranges and things like that. But none of it is evidenced base. If somebody asks me, I'll say, "Been there, done that." If you look at the history of Down Syndrome, they used to actually think that DS was caused by hypothyroidism – they didn't know about chromosomes until the 1960's. And so before that time, the prevailing theory was 'something is wrong with the thyroid'. And it was just because so many of the features of issues in the thyroid are similar to the issues that come with Down Syndrome: constipation, dry skin, thinning hair, developmental and educational problems, all that stuff which you can see in hypothyroidism alone, or you can see in Down Syndrome. That's why they used to say, "Well! Must be that everybody needs Synthroid!" so 'been there, done that,' like a hundred years ago, but now there's this new phase where people are saying the same thing again, it's like déjà vu all over again.

00:31:25 And then, what happens if you give somebody Synthroid when they don't need it is you can actually kick them into hyperthyroidism which is a real problem. It's no better than hypothyroidism in terms of something that you would want. So if you over do it, if you give your body more than it actually needs, you might be causing more problems – problems concerning even your organs – as well your endocrine systems. Most endocrine systems work where a product that is created is the same product that shuts it down so your body has this built-in mechanism that tells it to make something when needed, and stop when it has enough. When that system is out of whack, whether it's because of hypothyroidism or because you're giving a medication, you might be shutting things down along this pathway which might not be something that you'd want to do.

The main side effect, therefore, is not one thing; it's actually inducing hyperthyroidism which is a real problem. And there are many pockets around the country where families have questions; personally I think it's great. If you don't ask it, then we're not doing our job as medical people in responding to what's out

there. There's so much out there that many well-intentioned people want to be true. I know that I wanted more than anything for some of these trials to pass through about the recent issues with Alzheimer's. There have so many great theories proposed by doctors that say, "If we're going to give this medicine here, then it's going to make this better in Alzheimer's," and then almost every single time, it's like, "eh, not really." There's lot of times where things are out there in theories that should make sense but in reality, it might work in a mouse but not in a human – that type of thing. So yeah, whenever you see something on the Internet, always always always ask somebody who you trust with their knowledge and if you can't find somebody, email us.

00:33:38 The question is, "Especially in children under 3 years of age, what do we do about thyroid tests that come back a little out of whack?" And that's a really important distinction, too.

Between birth and three years of age is probably the most active time of brain development and body development that you'll have. People always talk about the growth spurt of puberty and all that kind of stuff, but truly you never grow like you grow in the first three years of life. I mean, think about what you come out as and then what you grow into by three years old – there's so much that happens in those three years of life.

In that age range, if I'm seeing that the TSH is at a 10.1, maybe in a ten year old I can say, "Well maybe it will go back to normal in a few months." If I see that in a ten month old, I would definitely be seeing the benefit of treating and making sure that the thyroid function is normal for those first several years of life is way more important than the risk of being on Synthroid. And so what do you do? And we have had that situation where there's an interesting phenomena – if your kid's ever had heart surgery in the newborn period – that Betadine that they use to clean the skin for heart surgery, it can actually throw thyroid function out of whack. I always tell families that it's always great to get blood drawn when you're in an operating room so they don't have to get stuck at the doctor's office. And it's okay to do it for the ear tubes and all that other stuff but heart surgery, where they're going to be throwing a lot of Betadine on the skin, always be aware that it can throw off thyroid function testing out of whack.

And then you're stuck with, well what do I do? I have a six month old with a thyroid test that's abnormal. Most people will wait for three years and then try to do the testing. That's a good tip really: try to not do thyroid testing during the periods of times where a lot of Betadine is going to be put on the skin.

But then aside from that, if that's not the case, if at three the child is able to come off thyroid supplementation, usually for the first few years after that I check more frequently just to make sure that they don't trend backward. But I would treat them the same way; I still wouldn't treat. Instead I would just say that we should watch that more closely, probably in three months I would repeat it because it's

out of the normal range like the thyroid antibodies, all of the stuff we were just talking about.

Audience: [Follow up question, unintelligible]

Dr. Vellody: You're not on enough Synthroid then. The TSH should be, because of this feedback pathway, the TSH should be very sensitive to thyroid hormone replacement. And so if it's still high, you probably need to move up a little bit more with the Synthroid. Now people with Down Syndrome tend to be very responsive to the Synthroid and so it's not usually a problem that we'll run into it's actually quite the opposite – usually I can just start them off on a very very low dose of Synthroid for the kids, much lower than I would for another child, and they seem to respond well to it. When you start the Synthroid, though, you don't want to repeat the test until about six to eight weeks because it takes that long for the body to acclimate to the new dosing. If you start today and check again in two weeks, it's not going to be corrected yet. But if you start today and check again in two months, then probably you need to go up a little bit in the dosage.

Audience: [Follow up question, unintelligible]

Dr. Vellody: I think when we get somewhere that is beyond what we typically see, that's when the endocrinologist can come in and make sure that there's not some other reason why they're not responding to the Synthroid. Usually with Synthroid – it's not like Miralax where doctors have a hard time finding the right dose – usually it's quite easy by comparison and usually it's pretty effective.

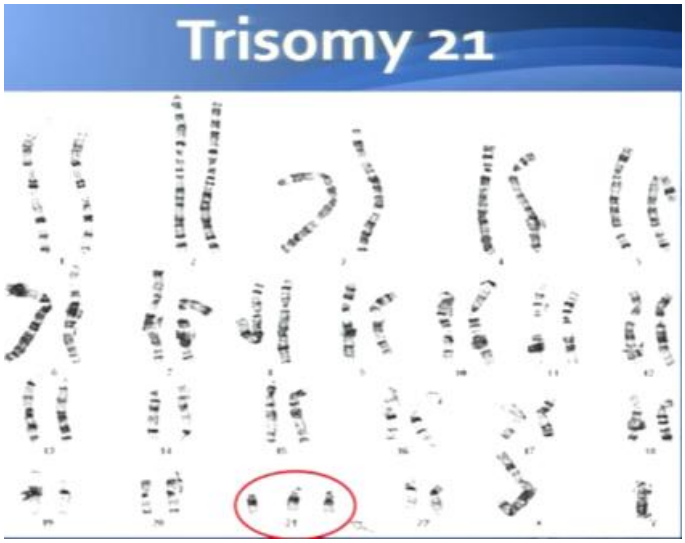
Audience: [Follow up question, unintelligible]

Dr. Vellody: Typically, the TSH does not go up when you increase the Synthroid – that is definitely out of the normal range of things that we see! I'm glad that you're seeing an endocrinologist about that. And he's 8 years old, yes? Certainly that is not an abnormal range for Hashimoto. A lot of those autoimmune type of conditions that we see, especially with the thyroid, 8 is definitely within the age range when we can see that. Management of it is simply the same as it would be for anybody with hypothyroidism, the Synthroid. It just lets us know that it's the auto-immune type. And the reason why that is sometimes very helpful is that it can tell us to watch out for the other ones. People with autoimmune hypothyroidism might be more likely to get Celiac Disease, or type 1 Diabetes, or Alopecia Areata which is that autoimmune disease causing hair loss, and so it's important that we keep a watchful eye out on all of that and those symptoms that can fit into any of those or another autoimmune condition.

00:39:32 The next question is, "When do you, or should you see a geneticist to go over the chromosome results?"

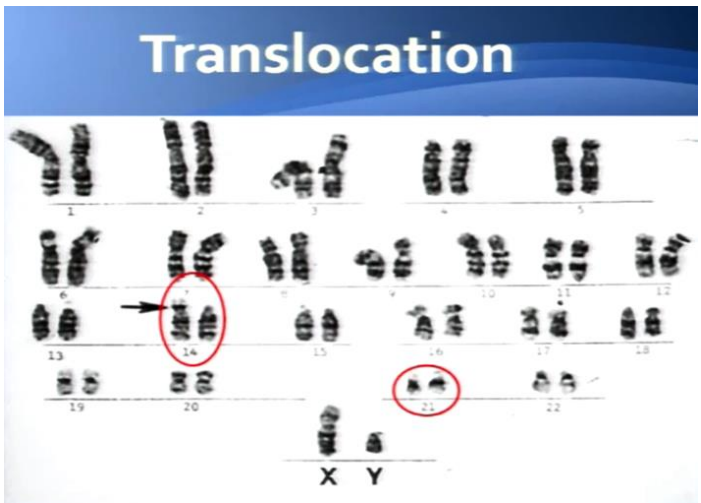
As most of you have maybe read in the past or may be familiar with the three types of Down Syndrome that you'll see. The most common type is where there's

just an extra chromosome 21 in every cell of that person's body – that is the case about 95% of the time. Then we try to find out where that extra chromosome came from. It might be from Mom, it might be from Dad. It doesn't really change what the



developmental outcome will be. But the reason we really check the chromosomes is first for diagnosis, but also to check for the second type that it might be – the Translocation type of Down Syndrome. In fact, I have some pictures here that show the difference between the two.

So this is 21 – this which the Down have.



the Trisomy is the case about 95% of people with Syndrome This a boy,

XY, two chromosomes because one of these comes from his mom, one is from his dad. But when we look at Chromosomes 21, there are now 3 of them. The reason why it's important to find out if you have this type is because this is the type that is not hereditary – meaning that it does not increase the chances of future pregnancies of a child with Down Syndrome, or increase the chances of a sibling to have Down Syndrome, or any of that stuff. This is not that type. It is not the one that runs in families.

This type though, this Translocation type, is the one that we were starting to allude to. This boy also have Down Syndrome, but although it looks like he has 2 chromosomes 21 like normal, the third one is actually where the black arrow is – it's actually added onto chromosome 14. You might've read about it where it's called Robertsonian translocation and basically the third chromosome of 21 is just attached to 14. Now why this is important is not from a developmental perspective. The kids with Translocation Down Syndrome will develop similarly and will likely have the same opportunities as anyone with the first type that we saw. But if we saw this, we would want to offer to the family the option of genetic counseling because this type is much more likely to run in families. We may find a situation like this in which the child's father has two chromosome's 21 so he does not have Down Syndrome, but one of his chromosome 21s is again attached to 14. So when he contributes the sperm to the fertilization of the egg, then the two chromosomes from each parent go together in the egg, then than child is going to have Down Syndrome. This is the type that is most likely to "run in families" and is the main reason why we do genetic testing on kids. From a genetics perspective, it would change things.

Now the last type is the Mosaic type of Down Syndrome which is the one that we know least about – that's why they have their own Mosaic grow, national group – we really don't fully understand what or why it happens. Mosaic means that some of the cells in the body have an extra chromosome 21, but some of them don't. And it means that after conception, either one chromosome 21 was lost along the

way of insert into cell lines, or chromosome 21 was added and then divided to make the rest of the baby. We don't know. But that one is very rare, about 1% will have that Mosaic type.

00:43:46 So then the question becomes, do we really need to see a geneticist? If it's that first type of Down Syndrome that we talked about – the Trisomy 21 – the geneticist's role would be pretty much to explain that and will give you a copy of the picture of what the chromosomes look like as well as the information from a medical standpoint. It is important for families to have a copy of that somewhere in their file – if you don't, it's probably a good idea to ask your doctor to give you one. There may be certain services that your child may qualify for just based on diagnosis alone, and having that chromosome report alone is basically your proof and can get you those services. And then it's also important to have it for your OB in 20 years when your other kids are having children to say "No, this is the type of Down Syndrome your sibling has," so you don't need to do any other invasive testing – unless they wanted to, of course.

00:45:05 Now if there's translocation type, I pretty much universally refer the families onto genetic counseling so that they can give their opinion on what are the percent chances of having a future child with Down Syndrome and would that change anything and things like that.

Audience: [Follow up question, unintelligible]

Dr. Vellody: In terms of the report, what you want to look for is something like this. 95% of the time it will say something like 47, boy XY or girl XX, and then +21. This is 95% of the time what you are going to see. If it doesn't say that, if it says something else – like maybe 46, XX – and then ARR 14/21, that just means that there's been a rearrangement of the chromosomes and that child has a 14/21 Translocation type of Down Syndrome. And then for Mosaic Type, we'll usually pretty clearly state in there that some of the cells have this and some of the cells didn't – it'll be pretty clear terminology. Whenever you read a genetic report, it can sometimes have some language in there that I wish I could change nationally, how people report chromosome labs. Like sometimes the chromosome report will have, in big giant all capital letters 'ABNORMAL' and what I usually do, honestly, is I tell the families to just cross that word off. There is nothing abnormal about their chromosome report and I really mean that. I probably think that people with Down Syndrome are more like what we should all act like. I mean, one of our Self Advocates on the board this morning at breakfast was like 'I think I'm going to run for president,' and I said, 'You'd be the best choice I could find!' and I asked him what his platform would be and he said, 'Well, equality for people with disabilities and a dance on Saturday nights!' I think if we implemented that, I don't think we would have all the struggles that we have, don't you think?

So yeah, take a look at your chromosome report and it should be fairly straightforward. If it's the top one, I was saying there, your pediatrician should be

able to run through it with you. But if it's anything beyond that, then you should probably think about a genetic counselor, just to maybe talk about the future.

00:47:40 The follow up question was, "If the child has Translocation type, does that automatically mean that one of the parents might or that the siblings might?" And it doesn't. This sometimes can happen just randomly in the child, and the testing of the parents just helps to know further if they carry it or if they don't. I forget the exact percentage but it is not everybody that's gonna have a parent who is a carrier.

One of the biggest changes to the Health Care Guidelines was around your question which was, "What do we do with x-ray? The neck x-rays. Does everybody need it or how do we decide who needs a neck x-ray?"

00:48:33 Atlantoaxial instability is what you're asking about. And it was a great question because it was a major change in the 2011 guidelines. Back in the early 90s, when they were first making healthcare guidelines for people with Down Syndrome, they recommended that everybody get an X-ray at around 3-5 years of age, and then at 10 years of age. And that was in the early 90s! Then in the late 90s, in 1999, they said that it was too many x-rays and said to do only 1 x-ray for everybody at around 3-5 years of age. Then in 2011, they changed it all and I'll show you why I think that was a good idea. Now they say to do it only if there are symptoms and we'll talk about those symptoms here in a second.

But this is what you're worried about in atlantoaxial instability. In your neck you have 7 cervical vertebrae – the little bones. What those bones are really there to do is to protect the spinal cord that goes down from your brain all the way to the lower part of your back. Those vertebral bones are there to protect it. That's why they have that circular shape to them and then down the middle goes the spinal cord. Those bones are there to protect a very important part of your body which is the spinal cord. The way it does that is, you have the top two cervical vertebrae, C1 and C2. They have other names for them: "Atlas" which I think comes from Greek mythology "Atlas who holds up the world" that sits right underneath your skull so it holds up the skull and holds up the world of your body; and "Axis " is the one right below it.

On the axis is this little finger kind of thing that sticks up called the dens. And what that does is, there are ligaments that hold this dens to the atlas. It allows your head to rotate but the ligament should be there to keep the bones from sliding upon each other. Now, anybody who's ever been with or worked with a person with Down Syndrome before will know that they have lower ligament tone. You might notice it in their ankles, how they are super flexible, things of that nature. That same ligament laxity is there sometimes in the atlantoaxial joint, that C1-C2 joint where the dens and the atlas connect. And so what happens is, if there's too much movement, then it can actually compress the spinal cord. As

you can imagine, spinal cord compression is a huge issue; you'd never want that for somebody if it was preventable.

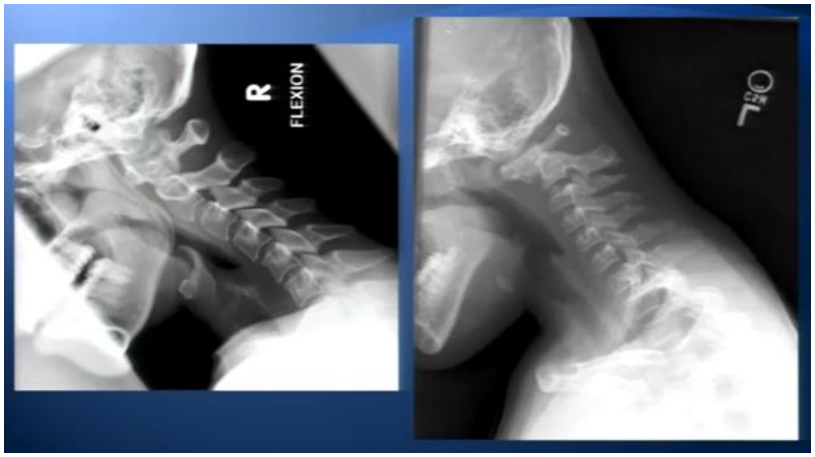
00:51:26 Therefore, Question 1 should be, "Should we screen for atlantoaxial instability in people with Down Syndrome?" If you look at people with Down Syndrome who get symptomatic atlantoaxial instability, symptoms would be neck pain, neck stiffness, arm or leg weakness, change in the way they walk, or if they've been toilet trained for a period of time and then suddenly lose control of their bowel bladder, those types of things. If you notice any of those types of things, that's about 1% maybe of people with Down Syndrome who will ever have any symptoms of atlantoaxial instability. But then if you x-ray everybody, about 30% will have an abnormal x-ray. So after that, you have all these kids with abnormal x-rays, you're obviously over-calling a lot – you've got a lot of what we call "false-positive" testing.

So yes, it would be great if we could find a good way to screen people with Down Syndrome imaging-wise that would be effective. But it's not. But then, here's what happens, you get an X-Ray, you're one of the 30% that comes back with an abnormal x-ray, then you get another x-ray to make sure that the first one wasn't just us catching him in a bad day so now that's two rounds of radiation. Then the radiologists – the images aren't going to be perfectly similar – is going to say, "Well they both kind of look like atlantoaxial instability." After that, your doctor is most likely going to send you to neural surgery or orthopedic surgery depending on what hospital system you find yourself in. Then the surgeon will say, "Well, we wouldn't want spinal compression, let's do an MRI," then the anesthesiologist will say, "Well we can't do an MRI on people with Down Syndrome without sedation. That sedation's kind of a risk because of the risk of sleep apnea so they go under general anesthesia which comes with its own set of risks. Then they get this MRI, the MRI comes back saying, "Everything looks great!" Of course the families will then go back to their doctors who will most likely say that they're worried about the abnormal X-Ray, "Well then, let's just keep repeating it every year!" And this just keeps on happening over and over and over again.

You see, people get uncomfortable whenever they see an abnormal reading in their chart that we're not doing anything about, even if it doesn't mean they're not ever going to have symptoms. And so this is a real, real issue that happened and that's why in 2011 the guideline said that they want a screening – because MRI is a great screening! – but first, we're going to look for symptoms of neck instability. If there are symptoms, then we'll get an x-ray and the positive predictive value of that test now goes much, much higher because the child actually has symptoms. So if there's an abnormality and symptoms, now it's a much more effective test rather than just doing it on everybody with Down Syndrome.

Audience: [Follow up question, unintelligible]

Dr. Vellody: Yes, here let me show you what these x-ray's actually look like.



The picture on the left is a normal x-ray; it is of someone who does not have atlantoaxial instability. The picture on the right, however, is of someone that does have it. Now remember, this kid is very, very severe but you can see how the C1 have slipped off the C2 so this child would definitely be having symptoms. This x-ray, I pulled from one of the girls that we saw from our clinic where this 4 or 5 year old little girl was holding her head in a particular way and I actually asked the parents, "Why does Rachael hold her head like that?" and her mom said "Oh, that's just torticollis. Now torticollis is a baby problem like when they get the flat head from always looking this way or that way; it's not a four year old problem. When I told her, "No, that's not right," we had the x-ray done and sure enough, it showed her C1 and C2 were slipping and we proceeded in the way that we always should. She had symptoms, we did the x-ray, it came back positive, and then we were able to correct it before she ever had permanent spinal cord damage.

If you identify this, in our institution at least, correcting it could be part of neurosurgery; but in some it could be orthopedic surgery. But what they do is, they go in there, they fuse the C1 and C2 and make it more aligned. Then for the next several months (it's no fun) but the kids have to wear this big Halo device so that they don't crank their neck back or anything like that – it's very challenging and a hassle and we would definitely want to avoid that. Preventing this is what we're trying to do but as of now, the x-ray is not a good way of diagnosing it or leading to treatment of it.

00:57:07 So the next question is about, "What would be your recommendations for limitations for people with Down Syndrome, because what if they have atlantoaxial instability or maybe it's intermittent or something like that, should they be able to do contact-type sports or anything like that?" And that's a really tough question to answer.

The one thing that the AAP Guideline says for sure is that kids with Down Syndrome should not be on trampolines without somebody who is trained with them – so like if a therapist wanted to use trampolines to help with gait or balance, that would be okay. And the reason why they have this fear, first of all, the American Academy of Pediatrics (AAP) has the biggest fear of trampolines out of anybody, really! And so, there's a lot of things that the AAP recommends that are really great but are just really challenging to implement in life like the don't eat hot dogs before you're 4 thing, and all this other stuff. But the trampoline thing, the first thing is that trampolines are what keep the ER in business! Trampolines and hover boards! Kids constant hurt each other or themselves on them because of all the games they play. One rolls over on the ground while the other ones jump on top of them or around them and the one jumps too high, ends up falling off the trampoline, that sort of thing.

Things that cause jarring motion to the neck or potential uncontrolled falls are things that we try to avoid in people with Down Syndrome regardless if they have a normal or abnormal x-ray. Even kids with normal x-rays can have atlantoaxial instability, again another reason why we don't like the x-ray so much. Abnormal X-Ray doesn't mean anything; normal X-Ray also doesn't really mean anything. So Special Olympics is the last sort of lingering group that has this requirement for the X-Ray but when we were talking about it in our medical group recently, it seems like that is soon going to be phasing out.

When I have this discussion with families, we talk about the risks and benefits. Is there a risk in playing contact football? Yes. There's a risk, I mean obviously, we've all seen the movie with Will Smith and all that. But even beyond the concussion type stuff, the risks for our patient population specifically is going to be the jarring the neck out of alignment and they might get spinal cord damage. Is there a risk in gymnastics - doing tumbling and somersaults and all that? There's risks in it. There's risk in everything. Now, at the same time, I ask the families, "How did you get to the clinic today?" You drove. There was a risk in driving! If you got into an accident, then the child's neck could of been jarred - that also is a risk. But it was a risk you were willing to take to come to the clinic. And so, it's the same kind of thing.

If your kid comes to you and says, "I love football and I love swimming!" Go to swimming. Try to push them in the direction of swimming because there might be just a little bit less risk involved. We actually have a football camp that we help sponsor because lots of the boys love football. And so there are benefits - flag football even - in that comradery as well as anyone who's ever played school sports or anything like that will tell you. You know that there's benefits in that especially when it comes to the social aspect of it.

Therefore, we know that there are risks for spinal instability but we know that there are benefits in participation, those sorts of things. But if your child, or a

child with Down Syndrome ever says, "No, I don't want to do that. It hurts my neck," this is not one of those times that you're going to be like, "You will eat your broccoli!" It's not that type of thing. If they said that activity hurt them, you shouldn't force them to do it again. I liken it to hitting that funny bone - when you get that shock up your arm and it feels uncomfortable and you don't want to do it again. If it's your neck and it goes down you're whole body.... If they say it hurts them, I would say that's not something to force upon them.

Audience: [Follow up question, unintelligible]

Dr. Vellody: Unless they say something to you about it hurting them, I can't imagine them doing it. In talking with people in our clinic with atlantoaxial instability, it's sometimes hard for them to verbalize what they are feeling exactly; it becomes hard to say. But if they're doing somersaults, and then they're doing it again, then odds are that it's not causing them any pain or discomfort. If they ever say it does, then I would say to stop, talk to your doctor, get an X-Ray.

Audience: [Follow up question, unintelligible]

Dr. Vellody: It's about 1% that patients will actually have symptoms of atlantoaxial instability. Does the risk of atlantoaxial instability change over life? Some of the things that we see in adults with Down Syndrome like bone weakness, osteoporosis, that kind of stuff, most likely can also impact the movement of those bones. I wouldn't want to set an age limit of concern for atlantoaxial instability - not a concern like you can't sleep at night, but a concern where if they say it hurts, then evaluate it. Or if they complain of arm or leg weakness coming out all of a sudden - we had a 17 year old that started walking with this strange sort of gait when a couple days ago he was walking just fine, and sure enough atlantoaxial instability was part of that as well.

Audience: [Follow up question, unintelligible]

Dr. Vellody: It was part of the question too which was, the other child got an X-Ray because they were going for an ENT surgery. If there is atlantoaxial instability, one of the reasons why the kids and adults want to keep themselves stiff or not want to move their neck is because they know that moving their neck causes them the pain and so there's smart enough not to move it. If you put somebody under anesthesia, you no longer have that protective ability and now you're essentially out, you're under the control of somebody else. And then, for tendon surgery I don't know if I would worry about as much, but for Ear Nose and Throat surgery they really have to crank their necks hard in order to get to those adenoids and those tonsils, to get a straight shot at them. Because of that, a lot of the ENTs will do one of two things. They'll say, "Well, we need to get an X-Ray," which we've just discussed - normal or abnormal really doesn't matter especially because the bones aren't really formed entirely in those younger ages, but even in a normal X-Ray doesn't mean "Don't be safe in the OR with this person with Down

Syndrome." And then, many of the anesthesiologists actually have an ability to measure nerve impulses in the lower extremities during surgery - continuous monitoring of those impulses. Most of the pediatric anesthesiologists are familiar with how to treat people with Down Syndrome and the risks of atlantoaxial instability, so they will offer to that patient this nerve monitoring during the ENT surgery which is great. If all of a sudden that nerve monitor starts to beep, we know instantly that we can't move the neck that way or do it where you're at but don't go any further, that sort of real-time information for the surgeon.

01:05:52 The next question was, and I'm going to need some clarification about the rash part, concerning a baby who has this neck stiffness kind of thing.

The rash, I don't know if that's connected. Probably the red spots though with the white are not connected but one thing that we do see at a higher frequency in people with Down Syndrome is plagiocephaly which is a big long word meaning 'flat head' on one side. In 1992, the AAP said to have all the babies sleep on their back so as to prevent SIDS - and we don't really know why but it works! SIDS drops tremendously when kids sleep on their backs. And for most kids, who don't have Down Syndrome, they're rolling around of course, they're sitting up around 6, 7 months, and so they're off the back of their heads. But for kids with Down Syndrome, many of our kids do roll a little bit sooner than normal because of that lower tone - it helps them roll around easier, but in terms of sitting up and walking, often times we're waiting a little bit longer for kids with Down Syndrome to do those things. They spend more time on their backs as kids and so they tend to get a little bit of flattening on the one side of the head. Because of that, the head will naturally turn to one side and the muscle will naturally start to stick in that position and that's what we call Torticollis.

Most likely, the reason why the neck is stiff in babies is usually caused by something like Torticollis rather than atlantoaxial instability. In babies, it's really hard to notice the instability because the bones, the dens, that project up from the axis is not fully ossified yet until really about 2 or 3 years old. And so, so you really can't assess for atlantoaxial instability by X-Ray - it's even worse in a baby because you can't see much.

If it's Torticollis though, somebody should be able to tell in an exam that it's just a muscle tightness thing - and the management for that is just physical therapy. Or, in some situations, not all, but in some situations they might do a helmet therapy to help to remold the shape of the head. But really, helmet therapy might just be on their way out - many people are starting to think that physical therapy alone may be enough.

01:09:07 The next question was about since the Doctor said that since you're having a child with Down Syndrome, you should probably just assume that they have atlantoaxial axial instability.

I look at that and I would modify it a little bit. I would say that it's always a good idea to be protective around the neck with people in Down Syndrome. Not because they all have atlantoaxial instability because they don't - in fact 99% of them don't - but because if you're always cautious and watching, then you're going to always be aware of those moments and tasks that do put them in pain, that do make them tell you that their neck hurt after doing that. I never tell parents to put their children in a bubble and not let them do anything. At the same time, I actually always tell parents that whenever a doctor tells them to limit a physical activity or something like that to always ask why. It's very uncommon that people with Down Syndrome will actually have atlantoaxial instability. And if the child wants to be active and do some flag football or something like that, as long as people are aware that the neck could be a potential problem and people are watching for it, then I don't think there's a reason that you have to restrict them from everything.

01:10:47 If somebody is not showing symptoms of atlantoaxial instability, and they're very active does that mean that they'll never be affected by it. And no, that's not the case at all. It's dynamic. Like we were saying, when you hurt your funny bone and there's that shock that goes through, that neck instability is a dynamic thing and sort of thing as well. There's typically going to be a movement in children with atlantoaxial instability that hurts them and they'll automatically know not to do. It's good as parents or as siblings to be very vigilant towards watching for those symptoms and recognizing them as a family member because it's an unfortunate thing but there are people in the medical field who have no idea about atlantoaxial instability in Down Syndrome. They might go so far as to say, "Oh, you've had an abnormal X-Ray," and you might respond with yeah, I had an X-Ray 8 years ago that was normal - it doesn't protect them, it doesn't mean that they're never going to have a possibility of having it. Because of that, it's always something to watch for - just like everything else that we talked about. You just watch for it, doesn't mean you have to lose sleep over it, you just have to watch for it. And if they ever develop any symptoms of it, you should evaluate for it. But no, not having symptoms now does not mean that they'll never have symptoms ever.

01:12:16 If the other ligaments on the child seem to be strong, does it mean that all of them are. And no, not necessarily, and even that sometimes changes over time. We have kids who at 6 to 9 months seem to have good ligaments from a tone perspective, then they get up and start walking and all of a sudden you see those ankles turning in. That's mainly because those ligaments in the ankle joint get all of our weigh - all of our weigh eventually ends up down there. And so you start to see those ankle inversions, things of that nature.

Having ligaments that don't seem hypotonic in one area does not mean that they're not going to be hypotonic in another area. It's not protective or anything like that.

01:12:59 There are two very important words to know the difference between when we're talking about muscles in people with Down Syndrome. There's "muscle strength" and there's "muscle tone". Muscle tone is your resting muscle movement or activity. Most of you here are awake! - but if you fell asleep, your head would fall forward. That's not because your muscles are weak; it's because when we sleep, we naturally lose our muscle tone which is our resting movement. The reason why you're upright and your head's not falling over or anything like that is because you're not actively telling your muscle to contract, but instead you have a muscle tone that is able to handle keeping your skeletal structure in place. Muscle strength, on the other hand, is a voluntary thing. What we see in people with Down Syndrome, especially when they're babies and they don't have a lot of muscle strength yet, is that tone issues are a bigger problem because they are always a little bit more floppier than the other kids. And I don't know if there's anything pathologically, if you were to do a muscle biopsy you would see, anything different in the muscles of somebody with Down Syndrome or without, but it's just that resting tone is less in almost everybody - especially babies - with Down Syndrome.

But then as they get older, the muscle strength starts to take over in terms of being able to overcome those lower tone issues that they have. Therefore, it's not like a twenty year old with Down Syndrome can't keep their head up or anything like that. We know that, we see that. It's not a forever problem - the lower tone - in terms of functionally being able to do things. But when you combine the low tone with the more flexible joints - especially like those in a baby - you notice a lot of that hypotone when they're smaller than when they're older

01:14:56 The next question, specifically, was about horseback riding or other activities - can they bring on atlantoaxial instability symptoms? And it can. It's again, that risk/benefit type of thing. The jostling on top of the horse, particularly if they start galloping or something like that, certainly can cause that jarring motion to the neck. It's reassuring when a child is doing horseback riding if they're not having any symptoms that things are going to be okay. But at the same time, a horse is a tall animal and a fall from a horse would definitely be something that we would try to avoid in somebody with Down Syndrome. Best situation, and safest probably, would also to have somebody by the side and not doing the heavy galloping that causes that neck movement. But if the child is doing it, and they're not having any symptoms, then it's a reassuring thing that that particular activity does not seem to be hurting them. But still, it's very important to keep that high vigilance up to look for any potential change in that at all - you'd definitely not want to ignore it. Just because it's never hurt before does not mean that it will never hurt in the future. And then, always evaluate it if you notice any new symptoms. Or if your doctor upon exam notices some changes in the things that we typically look for like strength, their reflexes in their lower extremities, things like that - if any change occurs, then definitely it should be evaluated further.

01:16:41 Then the last question which is a good one to end with is, "What do we do about getting information out to doctors to get them to be aware of the guidelines and what to look for and having questions?"

Really the best thing to do is directing your doctor towards where the healthcare guidelines can be found - that's for the doctors, that's for the parents - and bringing them with you to the visit and telling the doctor, "Hey listen, it says right here for a child between 3 and 6 years of age, these are the tests that we need to be able to do," and then they have to accept the fact that this is what the guideline says. It's not like Mom saying it; it's the guideline saying it! One of the things that we do as a regional Down Syndrome Center is we provide ourselves as resources to the doctors in our region, our community, and really anybody else who has any questions. They can always contact us, we have our email address there, they can also contact the NDSC who connects us with the professional advisory consul because maybe the question is not necessarily a doctor question but maybe they need expert advice from a national expert in physical therapy or something like that. So NDSC, we have a whole sleuth of people who, in their specific fields, are available to answer any questions that the doctors may have as well. So those are certainly options that you can use. And then you're regional Down Syndrome center in your region might also be very willing to share information with local doctors as well.

01:18:34 Thank you guys for coming! If you guys have any questions as well, by all means come on up. In the Pittsburgh area, we serve kind of the Eastern Ohio, West Virginia and Western Pennsylvania areas. The closest Down Syndrome center in our state is going to be in Philly and that's a good six hours away so we kind of share the state halfway between the two centers. Thank you once again for coming!

01:19:08 [End of Recorded Material]