

## CHARGE Syndrome Foundation

### CHARGing into the Teens Webinar transcript, November 11, 2012

**WEIR:** Well, good evening everyone. My name is Lisa Weir, and for those of you who do not know me, I'm the vice president of the CHARGE Syndrome Foundation. And on behalf of the board of directors for the CHARGE Syndrome Foundation, I would like to welcome everyone to this CHARGing into the Teens webinar. And I know that Randy just mentioned, but I just want to mention again if we can kind of save the chat box for the questions, it will help our moderators in terms of gathering the questions for the end. So that would be great if everyone could respect that.

It is my pleasure tonight to introduce you to our guest speaker. We are thrilled to have Dr. Kim Blake with us. And just a little bit about Kim, she began her involvement with CHARGE Syndrome 30 years ago at Great Ormond Street Hospital in the UK, where she lectured on CHARGE and published several of the earliest papers describing the syndrome. She was instrumental in organizing the UK family support group. And since moving to Canada, she has continued to be involved with the CHARGE Syndrome Foundation.

She's been invited speaker at every conference, and received funding from the foundation for several of her research projects. Kim's research career continues to focus on CHARGE, particularly, the issues of the adolescent and adult population. She routinely involves students in her research both educational and clinical. Most of her students have had abstracts or papers published. Kim has recruited many local medical faculty members in her research and developed the Center of Excellence for Research and Knowledge in CHARGE Syndrome.

She is regularly asked to present on CHARGE Syndrome both nationally and internationally. Her most recent research projects have included the effects of anesthesia, feeding difficulties in obstructive sleep apnea in individuals with CHARGE Syndrome, the clinical utility gene card for CHARGE Syndrome, and she and the team at the IWK hospital, in Halifax, Nova Scotia, are embarking on a new research project involving the ENT and genetics department involving the MBG scanner and looking at lower cranial nerve.

I've introduced Kim before, and I can't do so again without mentioning how instrumental she has been in our lives, since our own daughter was born. When we received the diagnosis almost 15 years ago, we felt very lost trying to figure everything out and thinking about what life would be like. Kim bounced into the neonatal unit, full of energy, positivity, and a let's get on with the attitude that really helped transform our thoughts on how this journey with CHARGE would proceed.

Kim does so much for the field of CHARGE in terms of everything I've just mentioned, and participating in webinars and training such as this one. But one of the very special things about Kim is her genuine connection to the families and the difference she makes to us on the very personal level. So thank you, Kim, for all you do, and we look forward to sharing this evening with you.

**BLAKE:** Thank you, Lisa. That was lovely. It makes me feel a bit a bit old, looking at little Kennedy there, no longer little Kennedy. Kennedy is all grown up. So thank you for that lovely introduction. And I want to say thank you to the foundation for supporting all of this. I listened to David a little bit before I came over. I wanted to see how he balanced the questions. And I wanted to continue listening to David's one and not come and do my one. So I've got it on hold to go back and relisten.

The foundation has been so supportive for me in my research. And right from the beginning, even the little bits of money, and the support that I've had both from the families, I couldn't have done it with all of you. And it has been wonderful watching your children grow up to their preteens, teens into their adulthood. So it is dating me a little bit, but I'm hoping to have some my students follow in my path. I've got Carrie Lee and Jilly, who is interested, so I'm hoping that they are going to come to the next conference with me.

So thank you, Kennedy, for the first pitch here. We, I started to put this together with the Olympics was on, and we thought, Kennedy at . . . would be a great introduction to the presentation. So Charging into the Teens, and here we go, charging. So just a quick thank you to my family and all the support. The picture up here, I'm just going to have a practice for the pointer to see if my pointer, oh, yes, my pointer works. So this is when my little girl who is now 15 was born.

And that was a Boston conference. And that's Joe and Ben. And Ben now is a soccer player. Joe wants to be a lawyer. Jessie is all grown up and looking taking all my clothes and borrowing all my things. And that is my husband who is very supportive and was getting all my technical things working out at home today so I can watch things.

So, objectives, I hope by the time we finish the presentation, that you'll have a better understanding of bone health and osteoporosis and probably some questions as well. Unscramble some of the puberty concerns. It's still quite a scramble there. I'm sure people have still got a lot to learn, but we will touch on that. Adolescent and adult data from not so recent anymore, but a research project that I did with Nancy . . . and quite a few other people and yourselves and future research interests. So let's carry on.

So osteoporosis, this is a lovely picture of McKenzie and Kennedy with my little pointer, McKenzie. Oh, come on pointer, come down here. McKenzie and Kennedy when they were at . . . and what is so lovely about their pictures is they always look so natural together. So they're doing stop/go sign thing, I think. Kennedy has got an IWK T-shirt on there. And why would you need to worry when they are so young? And I'm hoping some of you who are joining or some people that will watch this will actually want to do something about bone health from a very early age.

This is a great paper, if you are ever wanting to read about somebody growing up with CHARGE. Lisa . . . who is my, one of my students from a while ago now, wrote this. And she looked at Alan growing up with CHARGE. And I think we can learn a lot from your own children, case histories, and just people growing up with something complex as CHARGE Syndrome. This is Alan a bit more grown up. And I knew Alan from England, so Alan goes back a long way as far as I go back and David Brown goes back.

And we met at one of the family conferences in England for the first time. And Alan's issues into adolescent-hood let me to believe that there was a lot more in

CHARGE that needed to be uncovered from a very early, from very early times when I started to present. So I was always interested in the next problem, the next thing that we could look at, and the next challenge. So to me, the challenge would be, hormone levels, hormone replacements. Thyroid, the thyroid is another hormone that tends to be forgotten and always should be remembered.

Things like gallstones from an early age, Alan had a gall bladder out from a very early age, which is very usual. Reflux and oesophagitis, hiatus hernia, things that cause problems where you've got chronic reflux, and I think reflux, I remember speaking to Lisa, with Kennedy. And many of the other CHARGE moms and dads I spoke to, and I said feeding issues are going to be huge, and they will be ongoing. So this, to me is another feeding issue, and then the osteoporosis.

So if we take our little arrow back up there, thank you, green arrow. Osteoporosis. So bone is actually a living tissue. There's a lot going on with bone. We certainly need our bones. It's our skeleton. We'd all fall down if we didn't have our bones. Calcium phosphate are your minerals, and the collagen is protein. But what bone interacts with is a lot of things. It interacts with us being active, so activity. It interacts with hormones and, most importantly, the genetics. And then we've got lots of other things that we need to think about with bone. And so bone is, vital, and the demineralization of bone is disastrous.

So the risk factors that we're looking at with CHARGE Syndrome is we know about the delayed or absent puberty. And puberty can start and stop. People sort of see puberty starting and think, oh, great, you know, that is puberty. But it is the stopping and the starting or the not starting up which is a concern. Poor diet, again, CHARGE Syndrome individuals often have a challenge with their diets. So I really look at calcium and vitamin D a lot when I'm counseling. Inactivity. Just like David Brown was saying, the vestibular system is so important. Just getting active and having activities that promote bone health, we'll talk about a little bit more.

And then the growth hormone deficiency, which isn't so prevalent as being totally deficient, but we think that there are some concerns about using growth hormones, low levels of growth hormones.

So to measure bone density, we look at things like the DEXA scan, and these are machines that are becoming much more popular and much more available than when the, when I first even started my research in this. So a DEXA scan is measuring the actual density of the bones, the bone mineral density. And what you get with a DEXA scan, you get essentially a readout of what certain parts of the bone. So you get the upper femur, and then you get the vertebral spine, the spinal column. And that gives you a T and a Z score. So the T scores are what we see in adults, which we use in adults. But the Z score is children.

So anybody prepubescent, we would probably look at the Z score. But even with our kids with CHARGE Syndrome into their teens, because puberty is delayed, we may even still use the Z score. So you get a T and a Z score, and I expect that many of you have had this actually done yourselves, or your children may have had it done as well.

So the risk factors for poor bone health in adolescents and adults with CHARGE Syndrome, one of the risk factors is that we know that puberty is delayed. By delaying puberty when you're this age, which is actually 17 year on the graph, 17 years, your bone age may be actually delayed down to as much as 13, 14, 12 years. So this just

shows what your actual age is. When you look at your bones, this is your bone age. You get the bone age by looking at the, just the plain x-ray of the hands. So this, to me, is one of the important tasks, that I think that all young preteens, the teenyboppers, you know, so the 11, 12 should have done is to look what their bone age is because, essentially, it is often delayed.

And that's going to give you an idea of further height, further puberty, things like that. So this, to me, is a very vital technique. It's actually the beginning of tests. Before you even get a bone scan, a DEXA scan like we were talking about, this is a very simple test. It is just an x-ray of the hands, and the radiologists look at all the parts. They look at the metacarpals. They look at the fingers. They look at how the hands are growing, and they can actually date your bone age. The bone age is often in CHARGE, is different from your actual age.

So I can answer some more questions on that, if that's a problem, because that takes some understanding. I'm going to direct you to a paper that we did. This is when I was very interested. And papers always come out at a date, but they've often been done usually a good couple of years before this. And this is work that we did in 2005. And this is a really good paper to look at. And it is called, I'll think about what it says . . . it might be on one of the slides. Bone Health in CHARGE Syndrome, yeah, I remember it now, Bone Health in CHARGE. I'm not good at remembering names of my papers.

So our next slide, move that along. So from that paper that I've just shown you, we did some other, another paper came out, and that was scoliosis in CHARGE Syndrome. And what we found with that, the data from that paper, that scoliosis is actually prevalent in about 50% of the population that we were looking at. Kyphosis is another type of scoliosis, so essentially scoliosis usually at the top here, and that's the kyphosis and then bony fractures. The S shape is usually down on the bottom, and then bony fractures in about 30%. So not something that is low in numbers at all, so something that needs to be, we need to be concerned about.

And interesting with the scoliosis, just going back to the scoliosis, it's often the time when you notice the scoliosis is when the kids are growing rapidly. So after usually a gain around preteens during teenage time, that's when you're going to notice the scoliosis. So if there's a small amount, small amount of, so to look at scoliosis, I usually get the kids to bend over and touch their toes. And then if the spine looks, you can actually see that the spine is straight. If you got a little bit of a wiggle there, or you run your finger down, and it seems to divert on one side, that is something to really look for because that can actually increase over rapid growth. So that's something to be very aware of.

So again, a lot of these things I've been talking about, I think that you can look at preteen and preadolescent. So now, we've got the nutrition side of things. So again, this is dated from the paper I pointed out to you. So calcium, we found that 50% of adolescents and adults fail to meet what we call the RDA, the recommended daily allowance of calcium. So that's a lot, 50%. And then we've got 87%, and this is a very, this to me is a very important, that you've got essentially nearly the whole population of who we surveyed, not getting enough vitamin D.

Now this is interesting, because there's been a lot more papers. I was just reading about three or four different papers over this weekend about vitamin D being low in children with chronic diseases, chronic illnesses, with, when they're admitted to

ICUs, things like this. So this is actually, this is very, very important. And I think if you're going to take home one message from this is make sure your kids are getting enough vitamin D. We should probably all have more vitamin D except maybe the people in Florida because they get a lot of sun.

But we don't get a lot of sun up north. But again we tend to put sunscreen on our kids. The vitamin D has become much more important than me realize it was. I think it's always been important, but we realize it's important now.

So this is a slide if I point you to first of all, the top graph, what we've got here is, activity estimation. This is on a standardized activity form. And I think many of you that have actually joined in with my studies, and I've never got a lack of participants, and often it's your questions that I want to answer. So what we are seeing here is that we've got in the blue, we've got CHARGE individuals, and in red, we've got control. So what you are seeing here is weekday and weekend here. So that's weekday and weekend. So quite obvious you can see that the individuals with CHARGE are less active. So this is daily activity at this end.

So they are less active by substantial amounts. This is quite significantly significant. Then what we've got down here, is the age 19+, so with the age 19, we've got less of a difference but still a little bit of a difference. So it's this, and that is between the age of 13 and 18 that we see the most difference. This is probably low for everybody and needs to be increased. And that's why we've got obesity. But this is quite a worry.

So when we go back to Alan, which was quite again important for me to follow up and his problems in various research, we look at his age of 30, and that's his bone mineral density was low. And the bone mineral density is done by, as I said, a DEXA scan. So he was scoring in the actual osteoporosis range at 30, and he had a lot of the risk factors that I have been talking about. So for the prevention of osteoporosis, adequate diet. If you, there's apps and all sorts of things for everything. I'm sure there's an app for this as well. What we need, and this is for calcium, before you start to go into your teens or go into your preteens, 800 mg a day. And then, in the adult, in the adolescent, it goes up quite considerably because you're actually depositing bone.

And our adolescents with CHARGE will often go up beyond the 18 years, so probably up to 25, and then adults, we're looking about 1,000 mg a day. What you could do is get a dietitian to help you with this. I often have my dietitians in Halifax help me to look at the amount of calcium. But there again, it's probably quite easy to work out from just norm values. We all know that these are the sort of calcium-containing products. I always forget broccoli is a good calcium one as well. And then less so, and so more so is adequate vitamin D. And this you can get in drops.

What we are thinking now is 800 international units is probably too low. It's probably going to be 1,000 international units at least. This actually went up recently from 400, so if you see something that says that the osteoporosis can be prevented by 400 international units of vitamin D a day, it is certainly double that. And we're thinking it's more likely to be 1,000. Now the foods aren't so plentiful in our diet for vitamin D. So often, we need to add vitamin D in the tablets, liquids, gencaps, or drops.

This is a lovely picture of McKenzie and Kennedy on their swings. I really like it. This is one of my favorite pictures. I've got lots of pictures. So these are great for balance, great for vestibular, great for posture, but they are not great for bone mineral

density because essentially, there is no weight bearing. So to increase bone mineral density, it's got to be weight bearing. What's very interesting is, I don't know whether I've got it here, that, yes, elite swimmers have no increase in lumbar spine bone mineral density compared to sedentary individuals.

So essentially, swimming, when you are taking weight off of your feet, is not going to increase your bone mineral density. And that's why you've got to do dry-land training, as my daughter tells me all the time, I'm doing dry land. I'm like, do you really need to go at 5:00 in the morning? Yes I'm doing it dry land, mom. She swims. So bone issue relation occurs under what we call mechanical loading. So feet on the ground and some form of walking, anything that's going to give you feet on the ground, and anything that's going to give you what's called mechanical loading.

This is a challenge for some of our kids with CHARGE Syndrome. And as we know, many of them are often shufflers for a long while. What's been lovely to see in the conferences though, and it's been, I think I wish I could've taken a video of the very first conference with so many of the kids on their backs, sort of moving around, not moving around, really or needing to be pushed around in their stroller and things like that. Now we're got the kids with a little sort of push along with wheels, and I've been run down by a couple in the corridors. And I think it's really good. That is good mechanical loading.

So we'll just go on. Next one, so what we've got with prevention of osteoporosis. So adequate diet and exercise. This is a really important one, regular follow-up with the endocrinologist. I suggest to people that they start out with an endocrinologist as one of their key people from an early age. Jeremy Kirk will agree with me, the endocrinologist can keep an eye on good growth potential. And you think, well, anybody can measure height and weight. But if you've got one person measuring or a couple people measuring on one chart, one set of scales, you get a real accurate. So I would start them off from preschool age and get the endocrinologist to follow them after that.

If not, start before puberty, so eight, nine, ten, something like that. But it's really important that you have somebody, this is actually an important person in the team and tends to get forgotten. Although, I don't think that anybody could forget Jeremy Kirk. He's too present.

Sex hormone replacement therapy, really important. That gets missed, testosterone in boys and estrogen in girls. And we're going to talk a little bit more about that. And I would say seek physiotherapy and recreational therapy. We're just beginning to get somebody called the recreational therapist. Now I look to them quite a lot for my kiddies that are having problems with balance, or actually just being active. And being, creating different ways that can be more active, whether it's adapting tricycles, adapting ways of moving. So I'm looking at a recreational therapy a lot of my time when I'm consulting.

So the recommended daily allowance again for calcium, I would say 1,300, vitamin D 800, if not 1,000 units, and the hormone replacement. What is coming into discussion now is should bisphosphonates be used and should other drugs be used as first-line treatment for children who have essentially low bone mineral density or young adults? Certainly these are used in post-menopausal females. They've lost their estrogen, lost, essentially, ability to lay down bone because of the loss of estrogen. So

again, should they be use with our kids with the CHARGE? And I think that there is still discussion about that.

This certainly isn't the first line. This is the first line, but it's certainly something to think about. And it will be interesting to know if any of you are, any of your teens, young adults are on bisphosphonates. So we can talk about that.

So that's it for bone. And I've got some interesting questionings coming up there, so I think Lisa is trying to capture those. I can't do two, well, I can do two or three things at once, but I can't read quickly. Okay. Puberty, so unscrambling puberty.

The interesting thing is I was one of the people that got the LOL was lots of love. And thank goodness, I didn't use it in an appropriate way. And now I know, it's laugh out loud, I think, anyway. Don't like abbreviations very much. So being a teenager is not easy. I feel I've been a mom of three teenagers now, and I'll say it's not very easy. And I always think that many of the issues I go through, aren't quite dissimilar to some of the issues you guys go through. But I think you do a much better job than I do some the time. So let's have a look at adults and adolescents with CHARGE Syndrome.

So behavioral issues, I think I talk there, and I know I will let Tim talk about that more rather than me. Puberty stuff, I'm going to talk about, and what I talked about already, osteoporosis and scoliosis. This is a really nice first paper that we did on adults and adolescents with the CHARGE Syndrome, again with your help. And hopefully, the second paper might out before the next conference, which was a follow-up to this. So this is what you may see use in an endocrinologist's office. And these are Tanner Stages for females.

You can actually use them yourselves with your kiddies. They could actually use them with you, and you can see what kind of stages. What we tend to find is one and two Tanner stages, then the girls go into these stages quite quickly and then stop. So this will be, this sort of stage of breast development, so the budding stage, probably this stage of pubic hair, maybe not that. And again this stage, and then things stop, and they don't go on from there. And certainly there's no menstrual period. And they need to be started up again.

Again with boys, we often see a stop often at the very beginning. Nothing happens at all. There isn't anything. There isn't, it's just stage one, and they stay at stage one. Stage two usually has to be promoted by hormone treatment. We don't know how many people need hormone treatment who have got CHARGE Syndrome. We know not everybody. We used to probably think it was more prevalent. Now we're diagnosing individuals with what I call milder forms of CHARGE Syndrome. They're probably going to go through puberty. But they may end up again stopping and starting.

So those are what we call the Tanner Stages. And then, just looking at puberty, the best thing with the puberty is to start in the brain. So in the brain, you have what's called the hypothalamus, and you have the pituitary gland, and you have hormones that are released by the hypothalamus, call this one GnRH, gonadotropin-releasing hormone, and that then tells the pituitary to release its hormones, which is FSH and LH. So essentially, you've got a system of one gland telling another, by hormones. You could have any problem with any of these areas, down to the testes in the boys, down to the ovaries in the girls, and then you get the releases of testosterone and the estrogen. And then you get essentially puberty.

So there's a lot of, and this is very simplistic. So a lot of things can happen over the course of going into puberty. So again pediatrician is very important. I saw somebody say their pediatrician is, got rid of them because everything is going all right. I'd keep hold of your pediatrician even if it's just for a yearly check up. As you get older, the internist will probably take over or the adult endocrinologist is really important as well. So we know that we've got the data for this, and that gives you again the papers are worth taking in if you need to fight for something. And that's why I think publishing is very important.

So treatment, a kick-start is what we are looking for. And in the males, it is testosterone. I get a lot of my sort of, endocrine medical stuff, if I'm questioning it, from Jeremy, and he said, start on the low dose, increase. Same with the females, start on a low dose, and increase. The good thing about estrogen therapy, you can actually use the pill back-to-back pack, and you can actually stop menstruation for, you know, maybe four months, five months, and then have a breakthrough bleed. So it's actually quite useful for stopping the bleed.

So what everybody always asks me, and asks Jeremy, what about the concerns with hormone replacement therapy? We can talk of it more about it. But essentially, you got pluses on the side. I always think that if our young teen or teenager, young adult knows what T-shirt they are wearing, what speakers they are wearing, has a sense of themselves, a sense of, my daughter does nothing but put makeup on and brush her hair at the moment. Those sort of the things, then probably, they should have hormone therapy. If they are not interested, then I think there is some debate. But then, you've got to protect the bones.

So worsening behavior, weight gain could be a concern with hormone replacement therapy. But we're talking about replacements, not adding something that is not there. So it's not like taking the oral contraceptive pill for, as many of us who take it. Not me at the moment, I'm too old, but essentially for pregnancy or for pain during periods, and you want to try to have a lighter period. But essentially, this is replacement. So replacement is probably the very important word here. And then we're concerned with inappropriate sexual behaviors.

So low dose is probably the rule there. Being an adult doesn't get any easier as we all know that. And again, I will point you to a growth chart that we did with Alan. And what you can see is, here, we've got the weight, here we've got the height, and then the weight goes along quite nicely. And this is typical what we see of CHARGE, looking at sort of weight below the middle line, below the 50th, and traveling along, sometimes even underneath on the third or underneath there. Then things take off. And this is interesting looking at when things took off for Alan.

So he actually had a low BMI of 16.3. He ended up with a BMI of 34, and that's because his weight is going up there, and the BMI, you work out with, you do your height squared, in meters, divided into your weight. The weight is at the top in kilograms, and then height squared on the bottom in meters squared. And then you divide that one by the other. There is also an app for that as well. My students show me all the apps I don't know. I don't find them.

So we've got Alan's weight there, and his height there, and we ended up in a BMI of 34.5. So this is actually an obesity range. He's at reason for diabetes, heart disease, all sorts of things, and decrease in mobility and bone mineral loss. So this is a concern.

So again, like all of us, we have to watch this. And then, testosterone was started for a period of time to put him into puberty. And then again, as I showed you before, that is his bone mineral density. So these are the sort of charts that you can get from your endocrinologist, and they can be very useful.

I would suggest keeping one of these in your files, the nice sort of files that I think Meg Hefner and Sandy Davenport developed out of the CHARGE syndrome folders would be, this would be a very important graph to keep. And to plot height and weight as your children are growing, so they are growing along here to 6, 9 years, 11 years, and then using this to plot height and weight, as I said, not rocket science. I often wonder what rocket science is anyway. There's another question.

Okay. So adults with CHARGE Syndrome, medical problems to be considered with an older adult. When I'm presented with somebody who's older, with a complex condition, I often think, let's start from top to toe. So let's work sort of from here right the way down to see what's going on. And that could be very useful because I think if you've got somebody out of behavior, complaining, having problems, it's worth looking at the medical stuff first before saying, oh, it's just a behavioral thing. I never say it's just a behavioral thing. I actually think of things as doing, I do this sort of social, behavioral things that could be aggravating, and then I do the medical. And I always tell parents, I do both things at the same time. So there's sort of this more psychosocial stuff and then the medical stuff.

So reflux, gagging, coughing, hiccupping being a really, really common presenter of reflux refusing to eat. So think about reflux still even as an older person. Constipation. You could have liquid stool and still have hugely problems with constipation. And this is overflow. So sometimes you need a plain x-ray to look. But usually, that is something that gets completely forgotten and is well worth thinking and looking about. Celiac disease is more prevalent than we realize.

You can do a TTG. That's a big one to see that disease. I do a TTG and an IGA as well. Thyroid, very, very common, low thyroid or high thyroid. Heart disease may present as sweating, pallor, or tiredness. We know that a lot of our kids are growing up with congenital heart disease that has been fixed, repaired, or may need further operations. It's really worth, remember that, and they should be followed by an adult. There are specialists now that are coming into play looking at adult, the adult population with congenital heart disease. They really should be followed by somebody like that.

Deteriorating sensory issues, we all have that. And so these are things to think about, but most importantly with the CHARGE population, retinal detachment. Delay in puberty, we talked about that. And then down to the antipsychotic medication, too high, too wrong medication, too many medications is often one of the problems. One of my little CHARGE kids was just seen by somebody else. This is why it's always worth somebody else having another look, and they actually stopped some of the medications, which were prescribed, not by me, by somebody else. And did a lot better by stopping some of these antipsychotic and behavioral medications.

So adults and adolescents with CHARGE Syndrome, this is a study we started, Nancy Hartshorne, a few years ago, many years ago actually. I've still got my short red hair, so that sort of dates it. And we're still in the process of getting all of the results and finishing writing up. But I'm going to give you a few of the sort of important results that have come out of that study. So this is what we call health related quality of life, and . . .

tool that we use. And we looked at the U.S. data. Nancy did this for us, and then the CHARGE data.

And what we are finding, is actually things like quality of health, good to excellent, actually quite high in our CHARGE population considering how in and sick they are when they are little. Number of physical days unhealthy, not too bad, three, nearly four physical unhealthy days in a month. The number of mentally unhealthy days in a month, five, maybe a little bit more than the U.S. population. So that's your total, so not too divergent. We haven't got any norm values for the U.S., so we can't see whether it's statistically significant.

This is interesting I think. Looking at pain, CHARGE population is less than the U.S. This is one of the areas that we found with less. And that, I think, is something again to do with the senses and the pain and the sensory inputs. Sadness, anxiety, and sleep, maybe a little bit higher, but not too bad. And then we're going to go on to the new medical issues. Again, I think I'd like to draw your attention to the sleep apnea. I got very interested in that from probably this data and your questions. So I cannot, so a few questions on sleep apnea as they come up.

Retinal detachment, if there's any concerns about the eyes, this should be something to look at very seriously because of the coloboma. The other things we sort of touched on, seizures not being so high. Urinary tract infection is just one of those common things, shouldn't be forgotten, especially chronic urinary tract infection. So the conclusion that came from this work, which isn't published yet, but we've got data, which if you need anybody to, you know, if you want that data, we can share with you. Certainly be hopefully available at the next conference as well. Individuals with CHARGE syndrome appear to be fairly healthy in adolescence and adulthood. This is in stark contrast to their early days.

After sensory problems, which is the deafness, the blindness, and the balance, and then Tim would, and Davey would say vestibular as well. We've got sleep and anxiety. I'm very interested in the anxiety part of this, and I did have a little clip of video, but we didn't want to make me too technically challenged by showing it. Of Mackenzie, I went to visit Mackenzie at school, and I saw a big problem with her anxiety about transferring from one talk to the other, keeping up with everybody, and just pure exhaustion.

Her face from the beginning of the day to the end of the day was a picture. It was a picture of, I was putting so much effort, and I am absolutely exhausted now. Going back to the study that I was talking about, so we did some correlation analysis, and problems with sleep are significantly related to anxiety, self-abuse, and conduct problems and autistic-like behaviors. So when we looked at the sleep itself, correlated with the others, what we don't know is whether sleep problems contribute to those other thing, or whether all of these, anxiety, self-abuse called up problems as a result of sleep problems. Sleep again is very, very, very important. We all know how important sleep is. I think that has another huge aspect to health.

The future concerns for somebody like Alan, as he is growing up. And we saw, we started with Alan, are things to watch out for, retinal detachment, osteoporosis and fractures, raised BMI, psychiatric issues, and of course things like independent living skills as he is growing. The future research, it was very nice to hear Lisa say that I'm

still thinking of more projects to do on more research. I always like this slide because I'm very poor at keeping my controls away from my actual population I'm testing. So it would never work, Nicole. I am the experimental group, and you are in the control group. I hope some of you are laughing at that and may have laughed at me along the way.

So I've been very interested in the cranial nerves, as Tim Hartshorne knows, we've both been interested in the especially this nerve, the trigeminal nerve, which we feel has problems with migraines and probably problems associated with the feel inside the mouth and the swallowing, beginning swallowing mechanisms. These lower cranial nerves fascinate me. So I am interested in that aspect of CHARGE Syndrome to come. So overeating, I am hearing a lot of talk about overeating and sensory input to the oral cavity.

I just submitted to Maryland two abstracts. Actually, Kate pretty well wrote the first one. I'm going to present with somebody I never met, but sounds wonderful by e-mail. And we're going to present A Lot to Swallow. And then bone health, I'm going to present with Jeremy which probably Jeremy will do most of the presenting. But I always like presenting with Jeremy. And I want to have one of those big full audiences because I'm always presented usually on the other side of Tim and Jeremy. I don't end up getting as many people as them.

So look forward to seeing you all in the next conference next year, just around the corner. And I'd like to say thank you, and that is a lovely picture of Sharon and me. I don't know we're doing. I think I'm trying to do some tai chi, or, yeah, I think tai chi. Okay, I think we are doing well for time. It's ten to 9:00, my time, ten to 9:00. I had a nap this morning, so I could answer your questions. So I'd like to open things up for questions. Thank you.

**KLUMPH:** So, Lisa, if you would like to unmute by pressing star six, and I'm not sure who . . . read the questions.

**WEIR:** Okay. Kim, we have some great questions for you. Hello.

**BLAKE:** Hi.

**WEIR:** You got it, Pam?

**LORI:** Lisa, this is Lori. Go ahead, ask the questions.

**WEIR:** Okay. Kim, the first one is from Jessika, and she asks, is supplementing vitamin D drops in a tube-fed charger beneficial to helping prevent bone loss?

**BLAKE:** Hi, Jessika, that is a great question. Yes you can put the vitamin D in the tube, definitely, and it can be added to milk, the feed. It could be added to anything. It is pretty non, it doesn't have any real after effects to it. It's pharmacists, dietitians, people can sort of, you can consult. Definitely, you need more than the 800 international units. The more I have been reading, it is 1,000 international units that you will need. And that is probably going to look more than you might be comfortable with.

Get a dietitian to help you with that. Lots of information out there on this is the right way to go and especially as we're now sun blocking most of our children. And that is the other way to get vitamin D is through some sunshine.

**WEIR:** Great. Thank you, Kim. The next question, I guess, goes right into that. It was from Joanne. She wanted to know how to recommend increasing calcium for a child who eats baby food textures but no dairy and is partially G-tube fed.

**BLAKE:** So no dairy, and he's partially G-tube fed. Our kids really put us through it, don't they? So essentially, calcium can come, calcium, your regular calcium is actually in your Tums and things like that. It can come from various forms. It can be dissolved. It can be ground up. I'm just thinking of what I recently recommended to . . . chewable. Of course, a lot of our kids can't chew, but there are various things that can be added. Not, knowing that just looking back on my slides, that broccoli and things like that, sometimes there is actually good calcium in things that you wouldn't think have calcium in, so it might not be a bad idea to, and it does not have to be dairy.

So it might not be a bad idea to see, I'm always one to see whether it can be increased with natural ways in food. I am very, very prone to telling my families, this is not just the CHARGE, to go and visit somebody like a naturopath or somebody who can look at your diet in a little bit more detail. If you think about it in the hospital, we are often rushing around, and we don't have the time. And I find that somebody who's got time and can look exactly, I do what's called a three-day diet. I get the moms and dads to write out what their kids eat in three days. And then we look at that, and we see where we can improve, add things, whether they are getting the right amount of nutrients. So all those people can help.

But essentially, there are loads of ways of increasing without pure dairy. Does that answer your question, Joanne?

**WEIR:** Great I think most of the people are still on mute, Kim. But I think we have some good information there, for sure.

**BLAKE:** Oh, they can type in still, is that right, Lisa, they can still continue to type as well.

**WEIR:** Yeah.

**BLAKE:** Because I got a thank you from Jessika.

**WEIR:** Okay. The next one is from me. And I ask, do you recommend a DEXA scan routinely for individuals with CHARGE, and beginning at what age?

**BLAKE:** A DEXA scan, has Kennedy had DEXA scan actually, Lisa?

**WEIR:** No, she has not.

**BLAKE:** I mean, the kids that are coming along now that have had good nutrients, good bone health by essentially activities that are weight bearing, their bones are

probably in good shape. But it's and also going and getting hormone replacement at the right time. So do they need a regular one? Regular DEXA scans are useful if somebody has got low bone mineral density. So we'll call it osteoporosis, osteopenia is another name that's used, so essentially you can then track, like Alan had a number of them, and we tracked a long, he was tracked a long period of time to see whether the, by giving him extra vitamin D, by giving him extra hormones was actually helping his bones. Trouble is, once you get to that stage, it's quite difficult to rectify.

So what you would want to do is to probably get a baseline, so I would say one now when she's just in the middle of her teens is probably a good time. And then to plus or minus follow it depending on what the result is. So I would say beginning of teens, 12, 13, 14 is a good time to have one, and then to follow it depending on what that one looks like.

**WEIR:** Great, thank you. The next question we have is from Jody Wolfe, and she asks, have you seen any kids with CHARGE who have a bone age greater than their chronological age, and should this be concerning if there is no signs of early puberty?

**BLAKE:** I haven't seen anybody with a bone age that's greater. I would say that if it is greater, I would be concerned. I would be taking that to an endocrinologist. I would be discussing it, because that doesn't seem right to me. So and I would look to see what other medications they've been on, if there's been any other concerns with growth hormone. I've purposely kept away from growth hormone because people often confuse growth hormone with the sex hormones, the sex steroids.

The sex steroids are the FSH and LH, the ones I was talking to you about. And the growth hormone is released up in the pituitary as well. But people tend to confuse the two. But if you've got a bone age that's in advance, then that is different to what I've come across in the past. And I would probably be e-mailing Jeremy Kirk on that one as well because I'd like to see whether he's actually come across anybody with an advanced bone age who has CHARGE Syndrome.

**WEIR:** Okay. Great. Our next question is our endocrinologist discharged us and told us not to start coming back until our son is 13. Should we be followed still? He is almost eight.

**BLAKE:** I saw that question. I would say, can't you just see me on a yearly basis to plot and monitor growth, and, I mean, eight is a great time to start seeing an endocrinologist, and probably you did all the right things. And I think you go to my talks and Jeremy's talks, and we really push for an endocrinologist to be involved. And I would say maybe get a different endocrinologist if they don't want to follow. I very rarely say I don't want to follow somebody who's, you know, going to have problems in the future, that you think might have problems in the future.

They, you want to follow them before they get the problems. So, you know, to me, eight is a good age. What I said in my presentation, I dropped it down to even at a preschool age to just get the norm values of growth. You saw the growth chart. I mean, that's all to do with endocrinology. And then you can follow on. You can tell a lot by a growth chart, a well-plotted growth chart.

**WEIR:** Great. Our next question is from Joanne. Our endocrinologist essentially told us not to come back, oh, I guess she's just responding to the one above her. The next question is from Lori. Have you seen single-sided breast development?

**BLAKE:** Yes, that's quite common, Lori, in girls when they, actually, a lot of girls when they start puberty. Often one breast is more developed than the other, and it can stay that way. Most of us have slightly one sided, and some more than others. And so a little bit of asymmetry is normal. There may be more asymmetry because the upper body and the shoulders and the back with individuals with CHARGE Syndrome is sometimes asymmetrical as well.

Again, the cranial nerve actually, the cranial nerves do a lot more than we realize, and the back and the shoulders and trying to keep your shoulders hunched up, that's one of the lower, very lower cranial nerves, the accessory nerve. And I think all of that can make this part asymmetrical. But too much is not good. Again, endocrinologist is your person to have a look, and, you know, just hearing that doesn't negate from looking and seeing. And then that can stop. The puberty could stop there with asymmetry, and not go on again. I've actually lost my picture. Does that mean we've gone completely?

**WEIR:** No, you're still there, Kim, and you're still showing up for us. So it must just be on your end.

**BLAKE:** Okay. It's my mouse. I stopped wiggling my mouse. Okay. I wiggled my mouse again. So going back to that, Lori, a little bit is okay. The early start to puberty, it's okay. That can show that puberty stopped maybe, and nothing else is happening. That's not okay. What I said before, something really simple is to do an x-ray of the hands and look at the bone age. So then you know what real age the bones are at. Then that gives you a better idea. But again, I'll direct you to an endocrinologist that should be able to monitor that and help you.

**WEIR:** Great. Our next question is from Colleen, and she asks, how is the absence of sense of smell related to delayed puberty?

**BLAKE:** That's a really good question, Colleen. So essentially, if I can go back, I think I know how to do this, but I might just quickly flip back. Randy showed me a real quick way of doing it, but I'm going to click that one. What's very interesting, and it's something that has come from Kallmann Syndrome, which actually Jeremy is going to talk a bit more about, I think, in our presentation. And I'm going to put that as something that we will discuss. But the area here, the pituitary and the hypothalamus, when in embryology, when they're developing, especially this bit, the hypothalamus, the developing part is also developing around the nasal area, the nose area, the area where it's the sense of smell, sort of the optic, the olfactory nerve.

So those sort of develop together, and they develop really at the start of where the olfactory nerve develops. And this bit then develops, then gets sort of brought over from the olfactory nerve to develop over in this area. So they're well connected in

embryology. So the olfactory nerve, where your sense of smell, which is your first cranial nerve, all of this is developing together. Then this sort of heads off on its own, the hypothalamus, and then starts to develop, so that's very well connected. So there is, that's your simplest answer. So this GnRH is actually developing essentially around the same level, at the same anatomical level as your olfaction, as your sense of smell. Does that make sense?

**WEIR:** Yeah. All right. I don't see anything over in the window here. Okay. Next question, how often have you seen dysfunctional uterine bleeding in individuals with CHARGE, and what is the best way to deal with this for a young lady on hormone replacement therapy of low-dose birth control pills? And this is from me again, Kim. It's Lisa.

**BLAKE:** Hi, Lisa. Well, essentially, that's a really interesting question because I had the same issues with my daughter. And I went to see a gynecologist about that, and because she's a swimmer, and she wanted to have a pack of pills that sort of, she didn't want to have the bleeding. And she read about it, and her friends were on the pill. And that helped with the bleeding. So what the problem was, was the low-dose pills.

So the low-dose pills sometimes isn't enough, and what is happening is because it's low dose, you're getting these little breakthroughs, which can be much more frequent and much more distressing. So she probably needs to change the pill. And it's not really a high dose. It's just a different pill. And they can probably go back on the low dose once they've stabilized out. It's common at the beginning of puberty. So I learned that just as being a mother rather than as a pediatrician. I didn't know that before. I thought low dose would be the thing to use, and it sometimes isn't. So probably the right way to go is a regular pill to start with and then move on to the low dose later when they're stabilized a bit.

**WEIR:** Perfect. Thank you. Jessika asks, will a male born with no testes but has a scrotum need testosterone to push him into puberty, and what effects can this have on his puberty, growth, and maturity?

**BLAKE:** So that's a good question. That was from Jessika, is that right? So, Jessika, I like the way you spell your name, with a K as well. Yes, knowing whether boys are probably more likely not to go into puberty than girls with the testes problem. Sometimes the testes can be hidden away, and they need to be brought down. So knowing where they are early on is very important. So an ultrasound, a urologist beginning with you would be the person to consult with that and to make sure, sometimes the testes bounce up and down, and they don't come into the scrotum.

And they just need to be sort of what we call milked down to show that they're there. If they're not there at all, they could be hidden a bit further up, and you need to get an ultrasound. But then if they're not there at all, and they're not there at all, yes, you need hormones. And then that will do the regular job of putting the young man into puberty. How he feels about not having testes there, that's a really good question. I think you may have been getting at that. So implants and things like that can carry on. That's not my area of specialty. Again, a urologist is the person.

And a urologist deals with the sort what I call sort of the penis, the peeing, the testes, sort of that. You need a whole doctor for that area, and urology in girls, of course, but it tends to be a little bit more in boys. But that's an important part for boys, and certainly looks are very important, and I'm very conscious about that. I haven't personally come across adults with CHARGE that I've addressed that with, but it's something I've read about in the literature. And again, I would look to a urologist that would help with that.

**WEIR:** Great. We have an adult issue coming up next. Patricia asks, our son's recent hearing test has shown a sharp decrease in his hearing at age 34. Would you see this getting to the point of a complete hearing loss?

**BLAKE:** That's something I've heard about, and I think other people that are older with CHARGE can actually say that there is a concern with that. That needs to be monitored closely and certainly is very worrying. I think any decrease in senses, I know myself, just going, I've got to order those bifocal lenses and everything else so I can see properly. Any loss of, a little bit of loss of a sense, especially if you've got a challenge beforehand is a real worry. So that needs a lot of expert care and attention.

And there's certainly a concern that both vision and hearing can deteriorate. It can deteriorate in all of us. As we get older, it does deteriorate. Thirty-four is very young, but we know that adults with CHARGE Syndrome, a lot we're learning about now. So this may be something that's much more prevalent. I've certainly heard of this. And it's something, need to help me with names. I'm terrible. Who's our lovely audiologist that used to come to all the conferences? I didn't see him last time.

**WEIR:** Jim Thelen(?).

**BLAKE:** Yes, Jim. So Jim would be a great person to send a quick e-mail off to. I think he's still quite active, and I would actually ask him about that. He was quite interested in that area, I know, the last conference but one when I heard him speak.

**WEIR:** Great. Our next question comes from Sheri. And she asks, is there a benefit to a patch or a pill for hormone replacement therapy in girls? Is there an increased risk of breast cancer with the patch, especially if there is a familial history of breast cancer?

**BLAKE:** Hi, Sheri. That's a very good question. I think patch and pill, patch gives, absorbed in the skin. You're still getting estrogen absorbed. As far as, and they're still giving hormones. But I think the important part was hormone replacement therapy rather than extra. So you're really giving what the body needs anyway. With that history, you're quite right to be concerned.

And again, it's weighing up the advantages and disadvantages. I think again I'll say what Jeremy usually says, is give the little that's needed as possible, so the least amount that's needed, give that. That might be where the sort of low dose is advisable. But it's a replacement, so it's not adding more to the person. So there shouldn't be a risk. But the risk is the familial risk, so if there's somebody in the family, then that certainly needs to be ongoing screening for the rest of the family.

**WEIR:** Great. We have a question from Amrit, who says, Ama was assessed at Sick Kids three years ago, and it was determined that he did not require growth hormone treatment. He has not gained much height in the last three years. Do you recommend we revisit growth, sorry, the screen is bumping here. Do you recommend we revisit growth hormone therapy with endocrine at Sick Kids?

**BLAKE:** Yes, Amrit. I do. I think that that's something, once you're seeing a problem with height along, it probably means that testing should be redone actually. Again, sometimes it takes just watching and waiting to see something, you know, sort of appear. If you've got points, like heights and weights over time, and you can plot one of those growth curves or actually just bring them along, that could be very, so they would have had some, they would have done some workup on Ama before they discharged him and said he was all right.

So if you've got something in between that time that you can actually bring along, that would be very helpful. Sometimes GPs, something . . . from his regular pediatrician, but that definitely needs to be revisited again. And I've forgotten how old, he's getting along now. He's getting a lot older. So, you know, what? A regular follow-up on a yearly basis might be a good idea as well even if they put him through a lot of the assessments. He's 11. I got that. Is he really 11? Oh, my God. I remember when he was little. Okay. So, yeah, this is a great time. And then, you know, he's prepubescent, he's a teenie-bopper. He's going into teens.

**WEIR:** Great. We have another question from Jessika. She asks, can the lack of testosterone cause behavioral frustrations in a pubescent child?

**BLAKE:** Absolutely, Jessika. And that's one of my big, key things from many, many, many conferences ago that we shouldn't deprive the kids of what they need and the normal growing up, even if it does, I mean, there's always that balance. Is it causing behavioral problems? Well, I tell you what. Having had two boys and a girl, oh, my goodness, the hormone changes in my little girl are incredible. I don't open my mouth. I wait and see, what's she going to be like this morning or tonight or in an hour's time? Anyway, so the bottom line is, yes.

The bottom line, I can't think of what the question was. No, I do remember what the question, can the lack of testosterone, yes. I mean, it's, and the other thing about it is ongoing testosterone treatment into, once puberty has been hit, the question about would, should one carry on with ongoing treatment? Yes is the answer to that. My husband is an adult endocrinologist, and it's very, very, very important for self, for just, you know, even if you, we all get these fluctuation levels of hormones, especially us girls. But it's important.

**WEIR:** Great. We have a question from Maria who asks, is there a typical age boys with CHARGE hit puberty, and at what age do we intervene?

**BLAKE:** Boys with CHARGE often hit puberty a bit late. I mean, boys generally hit puberty later than girls. We know that. We know that for evidence. The girls, and

actually girls are hitting, girls and boys in our culture are hitting puberty earlier, and that's probably just because they're a little bit heavier, a little bit more overweight, or just more properly nutritionally fed. So a girl should start signs of puberty around 10, 11, 12. You're really concerned if you're not seeing anything, you know, gone 11, 12. Boys probably around I would say 11, 12, 13, so there's a shift for boys. So I would say if you're not seeing anything at 11, 12 in girls, be concerned. If you're not seeing something at 12, 13 in boys, be concerned.

So that should be about the start. And that's where you look at can, sometimes you get, I didn't mention that. Sometimes you just get the smell. You think of a grade six classroom, it's a smelly classroom, where they haven't learned to use deodorant yet. So it's with boys, you know, so you don't have to be looking at testes and things like that and trying to measure and look. I mean, that's really difficult to do. But it's the smell. You've got to have that sort of odor, which shows that you've started to sweat. You've started to go through puberty.

**WEIR:** Great. Sally Prouty asks, can you discuss more about the trigeminal nerve? Can this be a reason so many children are self-abusive? And if so, how can this be handled?

**BLAKE:** I think the trigeminal nerve, the fifth nerve, is very, very, very interesting. I don't think enough has been done about the fifth nerve. I just had a, I just had somebody with CHARGE Syndrome in my clinic. We've actually had two new people diagnosed as CHARGE Syndrome at the IWK, and again, I think it's because people are much more aware of CHARGE Syndrome. These individuals have got quite mild features and some atypical features. And one of them was very interestingly said to me, Dr. Blake, when sand goes in her eyes, she doesn't feel it.

So the trigeminal nerve actually, it's one of the senses, one of the parts of the trigeminal nerve that we test in adults is the sclera, it's your part of your eye just over the top of your eye, the very, very, very anterior part. So if you go, you've got your eyelid, eyelash, and then you've got the sclera. You go and swipe that as a testing for the trigeminal nerve that's intact. And so this patient, this is one of the ways we picked up that she may have CHARGE Syndrome. She said, well, she's not feeling it properly. One side was worse than the other, we discovered. And it's not an easy test to do because you've got to swipe a bit of cotton wool across the eye.

But again, asking a parent, do you feel that they can, they have a sensation there? There's the test of the trigeminal. Trigeminal nerve covers the sensory part of down here, so there's the first part, second part, the third part, so it covers all the sensory parts of the face. It covers a lot of what's going on inside the mouth as well. And then you've got things that Tim Hartshorne and I are very interested in are migraines. You've concerns with the initial part of swallowing.

So I think the trigeminal nerve is very interesting and needs more input. And we're hoping that when we do the, when we get this study off and running, so we've only had one conversation about it so far. But I'm hoping to get the ethics in my Christmastime that we're going to look at MEG scanning, and we're looking particularly at the trigeminal nerve.

**WEIR:** Great. Colleen asks, can you explain how the use and timing of both and estrogen patch and growth hormone affects scoliosis and kyphosis treatments?

**BLAKE:** Hi, Colleen. Yes, essentially, what you're looking at with scoliosis is it's more marked when you've got increase in growth. So increase in growth happens usually around, many times growth hormone is post in and post out. So if somebody had been growth hormone deplete, and then starting to get growth hormone, then that's the time when you're going to notice scoliosis increased perhaps, and you need to be more vigilant and watch that. I send my kiddies and people with scoliosis I'm worried about to an orthopedic surgeon. They do measurements of the x-ray. They x-ray, and they x-ray a different positions, and they do special measurements to look at how the scoliosis, is it progressing?

So growth hormones, when you start giving hormones like growth or thyroid or the sex steroid hormones, anything, any of those are going to promote growth. Anything that promotes growth is going to increase scoliosis. So say your child has not been eating well, and they've been just, been really tricky to feed them. And all of a sudden, something is done, or they pick up with their feeding and their eating, and that's going to have an effect on their growth, and that can have an effect on scoliosis. So anything really can have an effect on scoliosis that's increasing the growth.

**WEIR:** And also on scoliosis, I believe this is our last question. How often do you recommend x-rays of the spine to monitor scoliosis? And that's from Jody Wolfe.

**BLAKE:** That's a good question, Jody. Again, I think it depends on how bad is it. And again, really from our last question, from Colleen's question, is watch the rapid rate of growth. So if you've got some worries about scoliosis, and your preteen has just got onto some hormones and is starting to grow a lot. I always look at growing a lot, growing out of clothes. So, you know, the measurements are one thing. But, you know, when you've got to sort of change pants a couple of times that year, you know you're growing a lot. Then is probably needs to be monitored every six months. Other than that, usually yearly is okay.

But if there's rapid growth, I would say more like six monthly. And if they're, and if you've got concerns, don't hesitate. Go and see, now there should be a referral to orthopedics even if there's mild scoliosis so it can be watched and monitored. And then the other person that's really good at monitoring and watching sometimes is the physiotherapist. And I love the therapists because they have more time, and they can take more time, and they can explain things more. So my friends in tow, usually the physio, OT, and people like that. And OT does a lot of seating and things like that, so they can be really, they can help you guide things along.

**WEIR:** Great. Well, I don't see any other questions, Kim. So on behalf of everybody at the foundation, I would like to thank you very much for sharing your knowledge and taking the time to answer all the great questions we had tonight. I'd like to thank all of the, everybody for coming and participating in the webinar. And just want to remind everyone to stay tuned for our next webinar announcement, which is going to be coming in the next couple of months. And if you liked the webinar and any of the work we're

doing at the foundation, and you're not already a member, we would surely appreciate it if you would become a member and support the work we're doing at the foundation. Thank you very much.

**BLAKE:** Thank you very much, Lisa. Thank you again for inviting me. Look forward to seeing everybody in 2013, round the corner. Bye.