LP Doc Talk Session #4:
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Topic: Medical management for skeletal dysplasia, specifically achondroplasia

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Moderator: Welcome to LP Doc Talk. We are here with Dr. Michael Bober and he is going to answer some questions for us on medical management. So, Dr. Bober, welcome. Thank you so much for being here with us, and I'm going to just let you take it from here.
(On screen: Dr. Michael Bober is an expert on genetic disorders, Brittle Bone Disease, and Skeletal Dysplasia.)

Dr. Bober: OK, thanks. Good afternoon, everyone. So we have a list of questions that have been sent in so we'll just try to go through them one at a time here.

So the first question comes from someone in Ireland who asks, **"My son has Spondyloepiphyseal Dysplasia Congenita, or SEDc, and my question relates to the Biomarin drugs. Are they specifically for achondroplasia? If so is there any development on a similar drug for SEDc."** The answer to that question is, at this point, the Biomarin drug is aimed specifically for achondroplasia, perhaps down the road for hypercondroplasia, but really the focus of that drug is on achondroplasia and that has to do with the molecular mechanism of what this CNP drug is targeting in the growth plate. We know that the molecular mechanism for SED congenita is very different than achondroplasia, so at this point, it seems unlikely that the Biomarin product will move into attempted treatment for that dysplasia. I think it's important to point out that at this stage, this drug is experimental; it's in a clinical trial, and we really don't have a significant expectation about whether it will work or not; that remains to be seen.

Moving on to the second question, which comes from South Africa, **"Where can you find the dwarfism treatment? Doesn't it have side effects? Which food can a person eat that the food could or would support his or her growth hormone? What specialist can help with this kind of medication?"** So, dwarfism by definition is disproportionate short stature. It is a skeletal dysplasia, and as such is caused by changes in the genetic blueprint of the skeleton; these changes are really in the proteins and the genes and in the blueprint, and for the most part, children with skeletal dysplasia do not have any differences in their growth hormone production; their growth hormone levels are very typical. What they lack, however, is the ability to appropriately respond to the growth hormone that's already circulating. That's why growth hormone really isn't an appropriate treatment for someone with dwarfism. There is no type of food that's going to change the genetic basis of dwarfism, however, if someone does have malnutrition, or isn't eating well, certainly the short stature could be exacerbated. But if people have regular, healthy

diet, that is all that is necessary for good health. In general, the treatments that we have for dwarfism and skeletal dysplasia involve surveilling for and screening for associated medical or surgical problems and treating those problems.

The third question that we have comes from the Philippines and it says, **"Hi. I have I have an 18-month-old son who has been diagnosed with a metaphyseal chondrodysplasia Sedaghatian type. I was wondering if there is someone in your group who has the same syndrome and could tell me a bit more about it. Thanks in advance."** This is a very difficult question. I'm not quite sure how to interpret it because the dysplasia that often goes by the description Sedaghatian is really a spondylometaphyseal dysplasia not exclusively metaphyseal, #1, and #2, it's a dysplasia that almost is always lethal in the perinatal period due to pulmonary insufficiency and chest wall size, so I'm a little puzzled. I suppose there could be someone who has spondylometaphyseal dysplasia Sedaghatian type who is 18-months-old, however, the most likely scenario here is that this child probably has truly a different diagnosis than what is suggested currently. In trying to go forward and sort that out in a little more detail would be my suggestion to that family.

Which brings us to the #4 question coming from St. John: **"My 2-year-old with achondroplasia has excessive amounts of fluid in her ears! I know this is normal for Achons. However we went 6 months trying to clear an ear infection and finally did. But anytime we go for another hearing test, the audiologist looks in and says way too much fluid. She has tubes put in both ears. Are the tubes not working, or is it normal for her to still have excessive amounts with the tubes placed?"** So this is a question that really relates to middle function, or middle ear dysfunction in achondroplasia. This is a very common associated problem, and I do think this is the most likely surgery, and most frequent surgery, for people who have achondroplasia to have. So the middle ear can accumulate fluid; and some fluid can be serous and non-infected or it can be infected. If the fluid cannot drain properly due to the eustachian tube not working correctly, then this fluid can accumulate, potentially becoming infected. The typical treatment, once it occurs, is to place a small tube through the tympanic membrane to provide the fluid an alternative escape route. Ear tubes are extremely effective in doing this, so if the tubes are patent and in place, the fluid should be relieved. So this question suggests to me that this individual does not have functioning tubes. Tubes can have varying life spans. We've seen some patients where they're falling out a week after you put them in, and sometimes, if all goes well, they'll last even two years. So this is a situation here where, more than the audiologist, I think this child needs to go back to the ENT for someone to take a closer look to ensure that the tubes are actually in place and patent. I think that covers that one.

Moving on to the next question looks like from Amy in New Orleans, related to fatigue. She says**, "I have Achondroplasia. I am 4' tall and weigh 92 lbs. I am 58-years-old and work full time. I have had two back surgeries; one in 2009 and a second in 2012, both were to relieve pressure in my lower spine that was causing extreme pain and numbness. I exercise daily by walking, yoga,**

swimming or biking. I tire more easily than I would like to and am getting concerned about this. I am rarely sick and was discharged by my neurosurgeon a year ago. Should I be concerned in the increase in fatigue and decrease in stamina? Thanks for any direction." So, it sounds like Amy is in excellent shape at 4-foot tall and 92 pounds and certainly exercises and participates in activities, which certainly we all think is excellent for everyone to do. The types of lumbar back surgeries she had seem fairly typical and it sounds like this problem she's describing, this fatigue issue, is not going to be directly related to the lumbar spine. In fact, it may, or may not, be related to her achondroplasia. I think this is a problem that probably would be benefitted from discussing with just a primary care physician. So, we do know that people with achondroplasia can have obstructive apnea, so if she was not sleeping well, and having apnea, that certainly could lead to fatigue and tiredness. And then there are other issues, perhaps anemia or low thyroid levels, things that were just associated with being a 58-year-old that could potentially be contributing to this situation. So, this is a problem that could have an achondroplasia relationship, maybe, maybe not, but I think could benefit from just a primary care evaluation rather than some specialty evaluation.

The next question comes from Texas. **"What are they doing in the research and development for SED? Are they looking for a treatment?** Well, this certainly relates very directly to question #1 from Ireland. Again, the Biomarin product at this time is going to be very focused on achondroplasia and the FGFR3 issues. I don't know that there are specific therapies; there are some groups that are doing research with mouse models with collagen 2 opathies as it relates to SED congenital, but certainly these are in the very early stages.

The next question would be also from Texas. **"My son was seen by doctors in 2010. At that time the doctors stated he didn't fall in any category. I was in the Army when they sent us to see you all. What can we do to see if he has developed anything that puts him in a category? He is 15 now and 4-foot 2-inches. No one is able to tell us if he is going to grow more or not or able to give us any type of more information. I know that through the years his genetic doctor sent x-rays and blood work to the doctor who had had been following him those years, but now the doctor has retired and the new genetic doctor hasn't really told us anything except that he won't grow anymore. What can we send a new doctor to look at so he/she can give us an opinion?"** OK. So this question really is about someone who's a teenage who has probably reached skeletal maturity and doesn't have a clear diagnosis. The reality is that this happens more often than people suspect. There are something like 450 well-described skeletal dysplasias and certainly likely others that are not very well described. Usually radiographically, by looking at people's X-rays, we can group them into various subcategories, and often times we cannot be any more specific than that. My suggestion for this situation is to try and go back at some interval, several years apart perhaps, to genetics, to hopefully a skeletal dysplasia expert, who can take new radiographic pictures, look at those images, do a good exam, be familiar with the literature, and try and help categorize and classify someone in such a way that

they can make a precise diagnosis. You can look at X-rays to see if growth plates are open or closed. If growth plates are closed, then someone has reach skeletal maturity and this would be the final height. That is something that should be pretty straightforward to see off of some basic X-rays.

Our next question comes from India. It says, **"My nephew was diagnosed with Achondroplasia in November of 2012 and turned 3 in April of this year. Do we have any treatment for this condition? Suggest the way forward."** So, again for almost all of our skeletal dysplasias, the primary care strategies are screening for, and surveilling for, medical issues and then seeking treatment for those problems if they are present. So, in early infancy, in achondroplasia, we worry about things like critical foramen magnum stenosis, potentially hydrocephalus, the thoracolumbar kyphosis, and as children get older, usually the risks of those problems decrease, and tend to be essentially back to baseline by the time they are around 3 – 3 ½ years old, and by that time we'd be wanting to pay more attention to things like fluid in the ears, whether or not they might need tubes, obstructive apnea, and potentially bowing in the lower extremities. I think the key here again, as with all kids, is to try and seek out some specialized help. Try and find physicians who are familiar with achondroplasia and can implement these management strategies.

The next question also comes from India. **"Dear Doctor, I want to know about BMN111 for achondroplasia for my baby girl who is diagnosed as the same. Could you please give me information on how can I take benefits of the drug for my child."** So again, BMN111 is a synthetic CNP analog that is being produced by Biomarin and is currently in clinical trials for patients with achondroplasia. At this point, the trials are in phase 2 of what could potentially be a three-phase study. So, we're very early on in the process. We don't know with certainty, whether or not this drug is going to be effective in improving some of the clinical problems for achondroplasia. We don't know what the side effects will be. But the clinical trials are underway, and hopefully in the near future, we'll have answers to those questions and can determine whether or not this is a potential therapy for some of the medial problems of achondroplasia. Again, we know much about achondroplasia and it would be important for you to try and take the child to a specialist so the appropriate screening and management plans can be put into place.

The next question comes again from Texas. **"Is there any medicine or cure for achondroplasia? What are the chances of having another baby with another form of gene mutation if you have one achondroplasia boy?"** So, the first question, again relates to, I assume, this BMN111, which I think has been answered. There is no cure for really any genetic condition, but there are really many ways which we can manage and treat those patients. And certainly, there are well-established treatment protocols, screening protocols, management protocols, for kids with achondroplasia, and again I would hope that there are specialists who are helping to take care of this child. The second question is relating to recurrence risks. So, if we have two parents of average stature and they have a child who has achondroplasia, the recurrence risk for that particular couple would be

approximately two or three percent. The reason being, typically we think of achondroplasia and other new dominant conditions for a family as being caused by a spelling mistake in either the sperm or the egg, which occurs at the time of conception. If that were in face the case, the recurrence risk should be the risk in the population, which we would estimate to be about 1 in 20/ 1 in 25,000 births. However, it is possible that the spelling mistake did not occur at the creation of the sperm or the egg, but rather in tissues that created the sperm, or in tissues that created the egg, therefore the next sperm or the next egg may also have the same spelling change. And we you know empirically, that is from counting families, that this can occur about two or three percent of the time. So again, in average parents with one child with achondroplasia, the chance of having a second child with achondroplasia is not the original 1 in 25,000, it is approximately two or three percent.

The chance of having a child with a different form of dwarfism is the same as the population risk. So those, depending upon the dysplasia, could be 1 in 25,000, 1 in 100,000, something like that.

Another genetic question comes from Poughkeepsie. **"Is it true that there is an increased risk of chromosomal abnormalities in the offspring of a couple who already have one child with Achondroplasia?"** The answer to this question directly would be "no," that these two things would be independent. There is probably a asterisk that needs to get added on to that which is to say that we know that as fathers age, they have an increased risk to have children that have new dominant mutations, which is what achondroplasia is. We also know that as women age, they have an increased chance to have a child with a chromosomal abnormality. So the relationship has to do with the age of the mother and the age of the father and not at all with the achondroplasia directly.

The next question also from New England, **"When working with physical therapists through early intervention who may not have experience with/knowledge of achondroplasia, what should I, as the parent of a little person, instruct them to watch out for or keep from doing? For example, when is assisted sitting an OK exercise? How do I know if something is pushing my child too far or just enough to assist with strengthening?"** Well, this is an excellent question actually, and one which I think is very important. I will say that there are definitely some differences of opinion regarding this however, my belief is that the typically developing child with achondroplasia should not, should not, have physical therapy. I think the risks of the therapy, as the parent points out, are far greater than the potential benefits, and we council our families in the infant period that physical therapy should not be done. This has to do with several issues. #1) People with achondroplasia have larger heads, shorter necks, which creates different mechanics. They develop gross motor control at different ages and at different patterns than typically developing kids. Often these different patterns are misrecognized as delays because of the critical foramen magnum stenosis, I really don't want people trying to do head and neck exercises on these infants until they

gain head control by themselves, which occurs usually at their own rate and much, much slower than the rate of a typically developing child. In fact, for achondroplasia, it's common for kids to roll before they have head control, which is a very different pattern than in a child who does not have achondroplasia. To put them in sitting positions exacerbates the risk of thoracolumbar kyphosis. So, for all of these reasons, we really just discourage physical therapy. We let the children develop at their own pace. There are age appropriate developmental gross motor scoring scales that can be used. I know these are available through the LPA online and I would suggest that the family, the pediatricians, and certainly is therapists are involved, they take a look at this carefully.

The next question is a series of question. **"If a child has no decompression issues, are they out of the woods as an adult? If not, what are signs to be aware of and should achondroplasia patients have MRI's every so often?"** I believe this question refers to the foramen magnum, and the answer to this question is usually we think that as people get older the likelihood that critical foramen magnum stenosis requiring decompression need be done goes down. We think the risks are highest during the first two years of life and then they gradually go and fade out. Certainly, we do have or have had older kids who have needed decompression, but I would certainly think that after they have reached skeletal maturity, there really is no risk for foramen magnum stenosis that would require a decompression. Now, whether or not someone needs foramen magnum decompression is very independent of whether or not they may or may not need lumbar spinal decompression surgery for stenosis there, which is almost always a problem of adulthood rather than childhood. In terms of routine "baseline" MRI's, that is not something that we do routinely in our practice. We take images when we believe that problems may be present based on physical examination history, or for other reasons.

Do kids with achondroplasia have growth spurts like average height kids? In general the answer to that question is no, they do not. If you look at the achondroplasia linear growth grids, you do not see a bump in the curve, so as a population this does not seem to occur. Certainly there are individuals who may move slightly up on the curve during this period, but in general there's not a clear-cut growth spurt across the population. We believe that this is because the hormones in the body, while they may be pushing the system, it's the growth plates ability to respond that's impaired and just because there's more growth hormone circulating doesn't mean that the growth plate will be able to respond any better.

Do the bones of children with achondroplasia heal faster than average height bones? Does it make a difference between girls and boys? The problem with achondroplasia is really in the growth plate cartilage, at this point there's no reason to suggest there's any difference in the bone structure. I would not think there's any difference in bone healing between typically developing kids and achondroplasia children and certainly not between boys and girls.

Do you know of any differences between people with G to A achon mutation vs. G to C achon mutation? Have any differences been noted? This refers to the individual spelling mistake inside the FGFR3 gene. Achondroplasia is caused by changes where the G goes to A, or the G goes to C at this one particular codon, regardless whether or not the change is to A or to C, it results in the same protein substitution; it creates the same missense mutation, so that we would not expect any differences to be present because the FGFR protein is the same in patients that have either G to A or G to C mutations.

Is there any connection between hypochondroplasia neonatal seizures and learning disabilities? So this is a very complicated question. So one at time: hypochondroplasia is not often recognized at birth. Often times kids come to attention between 3 and 5 years of age. We do believe that there is a relationship between hypochondroplasia and various learning disabilities, which can become recognized at school age. There is certainly a relationship between seizures in the neonatal period, which often result from low oxygen levels in and around birth and subsequent learning disabilities. So, there's a relationship between those two things that's independent of hypochondroplasia. We also do know that people with hypochondroplasia may have a very small risk of having a specific type of seizure often originating from the temporal lobe, or temporal lobe epilepsy, but usually this does not present in the neonatal period, but at a much greater age so this is a very tricky question to answer and I'm not clear what the question is really trying to ask. But there're definitely relationships between these things, but perhaps not all related, and not all three of them together.

And lastly, we'll go back to New York for a question that says, **"My daughter has achondroplasia and suffers sever leg pain at night. Is there anything you can suggest that will help her?"** So, this question illustrates a point in that it's important to try and understand exactly what is going on. So leg pain is very nonspecific. Is pain in the joint? Is it in the knee? Is it in the ankle? Is it in the thigh? Is it in the shin? So different places would suggest different kinds of problems. People with achondroplasia certainly can have bowing of the lower extremities, and bowing in the lower extremities can lead to joint pain, probably most likely in the knee, but it could referred down to the ankle or up to the hip. So if the pain was in a joint, trying to understand whether or not there was some type of bowing or other knee issue would be important. If the pain is in the mid-tibial region, these can be typical childhood growing pains. They tend to be transient – that is they don't last for long periods of time, but they can be quite painful while present. They tend to go away with time and respond to things like massage or some Motin. Lastly, although typically not severe, if we do have a child with achondroplasia who is quite active and trying to keep up with their peers, they often can develop fatigue, just muscle soreness, towards the end of the day. So to try and figure out the best way to help is to figure out what is the quality and location of the pain.

So I think at this point, this appears to be all the questions that we have. Thanks everybody for your attention. Good afternoon.

Moderator: Thank you, Dr. Bober so much for being here today. Thank you for donating your time. And thanks to everyone who joined us. Does anybody on the call have any questions they'd like to ask? Hearing none, again, thanks so much for being with us. Anyone can revisit this session recording on our website at www.GrowingStronger.org and click on the LP Doc Talk link. And you can find a recording of this session.

Watch for our next session in mid-December where we'll be talking about issues with school and bullying.