Ali Guermazi, MD, PhD  Good morning. Today we are going to talk about the paper that is going to be in the issue, July issue, of Radiology titled “Diffusion-Tensor Imaging of the Physis: A Possible Biomarker for Skeletal Growth—Experience with 151 Children.” I have the immense, the great pleasure to have the corresponding author with me today, Professor Diego Jaramillo from the Miami Children’s Hospital. He is an Associate Chair and Professor of Radiology there. So thank you Diego for being with us this morning and my first question would be can you explain what prompt you to conduct this study?

Diego Jaramillo, MD, MPH  This study is actually the culmination of a number of years of work. Initially we started working on animal models to look at the tensors in the physis and it seemed promising so we started taking some – because we were doing some diffusion studies on regular patients so we would then do the diffusion tensor images and process them in the physis and we noticed that you could actually look at the columnar architecture of the physis and the good thing of this is that with conventional MRI you see the physis as a series of layers, but functionally the physis is really a series of columns and that is what the diffusion tensor imaging information provides us with. We thought that we could then start looking at children and we noticed first that, and this was in a study published in Radiology in 2014, we noticed that the tensors were longer in the femur than in the tibia and this is what we would have expected if they would reflect rate of growth because femoral growth is greater than tibial growth, and then within the femur the growth was greater in the periphery than in the center which is what we would have expected as well. That made us think that the modality could be used as a biomarker for growth. So then we took a cohort of patients that were having MRIs for other reasons. We excluded any patient who had pathology and then we performed diffusion tensor imaging on these patients and then recorded several parameters age, gender, BMI, etc. and then we noticed that there was a striking correlation between growth or expected velocity of growth in a number of the DTI parameters.

A.G.  This is actually amazing because you started in 2014 it looks like with animal model and the discussion of this study that you published and can you just explain in more detail what the findings are, like briefly and why they are important?

D.J.  The length has been shown histologically that rate of growth depends on the length of the columns of converse lengths in the physis. We noticed that the tensors not only extend into the physis but also into the metaphysis in the newly formed bone. But still the column of cartilage in newly formed bone corresponds to the rate of growth. And so when you start looking at DTI parameters to make the length of the tract or particularly the volume of the tracks, they correlate well with the expected growth. So then we looked at the patients and we noticed that in our population the girls started having longer and longer tracts as they approached puberty and so by age 11 they had a peak and then the peak came down. Boys had the same findings but two years later. These are the same findings that we see for example in the Tanner growth curve where the greatest speed of growth is in girls around 11 and in boys around 13. And then we looked at other parameters, for example ADC. Interestingly ADC does the same thing, but a couple years earlier. But then we also looked at short patients versus tall patients that were greater than the 50th percentile. Of course the tall patients had longer, and this was particularly true in girls, the tall girls had longer tensors and larger tensor volumes than the short girls. We haven’t done a longitudinal study but it seems to be related to speed of growth.

A.G.  You said it well. It looks like this is adding a layer to what the x-ray can inform us about bone growth, so what is then the real add value of your described method?

D.J.  The real added value is that you could have a biomarker for growth and have more information about two things; how much growth there is going to be, and secondly is there physis getting too close to physeal closure so is there no more residual growth left. The importance of this is for example with therapies like growth hormone where we administer growth hormone in patients and it takes about a year or sometimes two years to determine whether there is response to therapy. Growth hormone costs approximately $50,000 per year. If you could identify the subset of patients that are responding to therapy after a few months, then you could decrease potential complications from therapy and also save a lot of money.

A.G.  This is absolutely great idea. I do think as an application for growth problems is probably one of the most challenging problems we have today and having a
biomarker like this one would be absolutely fantastic. Then it comes actually to the next question which is obviously if you have this idea about implementing in treatment in patients with growth problems, do you think this method can be easily implemented everywhere or do you think the method as any others comes with some challenges and if there are challenges, can you just tell us about them?

D.J. We have used off the shelf products, so this is the diffusion weighted sequence, we used – all the imaging was done at three tesla on Siemens three tesla units and using the conventional diffusion sequence that you can get on the magnet with 20 directions and b values of 0 and 600, so it’s something that is readily obtainable really in any of the MRI units. Incidentally we did obtain similar measurements at 1.5. So it’s not exclusive to 3 tesla imaging, you can get pretty good imaging at 1.5 as well and also and then the reconstruction is done with software called Trackvis, but you can use other software to reconstruct the tensors, but again I mean this is something that is readily available. The tricky part is when developing the expertise to sample the right area of the physes, but this is something that I mean several on our team have become very proficient and it’s – I mean it’s not immediately easy, but it’s not terribly difficult either. I mean it’s not that more difficult than performing 3D reconstructions for example.

A.G. Okay so if I understand you well you use it in specific situation at this point?

D.J. Yeah so right now we’re conducting a study, an interesting study, with survivors of neuroblastoma, and these are patients who have a lot of growth problems afterwards and many of them require growth hormone administration. Interestingly, we’ve seen that the for example the fractional anisotropy is very different for the neuroblastoma patients than for the controls in that the patients who have less growth have shorter tensors, a more disorganized growth plate and they don’t have as a high NADT so all of these parameters that come from the DTI seems to be correlating well with the rate of growth in the patients who are receiving growth hormone and that are having growth problems in the case of neuroblastoma. The plan, a little bit longer term, is to follow a cohort of patients who are short and who some of which have growth hormone deficiency and some of which don’t, and also to do a longitudinal study in normal patients because one of the things that we don’t have is longitudinal data. We don’t have – we have cross sectional data from a lot of patients, but we haven’t followed patients let’s say for two or three years and that’s another thing that we plan to do.

A.G. Very interesting and I’m looking forward to the next data longitudinally. I hope that you’re going to just think about Radiology and to send it there.

D.J. Of course.

A.G. Looking forward to it. I have my actually, I do think we are in the last question and I really, I mean I’m actually have been doing some pediatric radiology in the past, MSK, and to me is actually the bone age is a big issue that is very important. So do you think we can use, with confidence, this method in resolving bone age issues or simply your method just focuses on skeletal maturation?

D.J. I think at this point we don’t have enough data to have that degree of reliability. I think one thing that we can predict with a lot of certainty is whether there is growth potential or not, but beyond that in terms of dating the growth plate or the skeleton, I don’t think we’re quite there. One thing I was going to say is that another application going forward will be for example in patients who have chronic injuries to their growth plate, the thing that comes to mind which his very common is patients who have suffered chronic physeal injury due to sports; gymnasts, baseball players, etc. Again in these patients it’s very important to know, should they stop their activity or is there a damage to the growth plate or can they continue exercising. Again, that’s another area where we would like to explore. But in all these cases I don’t think we have enough data yet to really know with certainty for example what is going to be the growth in the next few years and so the only thing we can say with certainty is there growth potential or not.

A.G. Thanks Dr. Jamarillo, thanks Diego. It’s been a pleasure talking to you and thanks very much for joining from Switzerland. This is tremendous work and it’s very exciting and I’m really looking forward to some longitudinal data that we’re going to receive hopefully in Radiology. Thanks again.

D.J. Thank you.