Quantitative Analysis of Prostate Multiparametric MR Images for Detection of Aggressive Prostate Cancer in the Peripheral Zone: A Multiple Imager Study

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Prostate Cancer: PI-RADS Version 2 Helps Preoperatively Predict Clinically Significant Cancers


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Herbert Y. Kressel, MD  Hi. This is Herb Kressel, Editor of Radiology. Today I am joined by Professor Olivier Rouvière, who is Professor of Radiology at the University of Lyon in France. Professor Rouvière, with his colleagues, have authored a very provocative study entitled “Quantitative Analysis of Prostate Multiparametric MR Images for Detection of Aggressive Prostate Cancer in the Peripheral Zone: A Multi Scanner Study.” Welcome Professor Rouvière.

Olivier Rouvière, MD, PhD  Hello.

H.Y.K.  Thanks very much for joining us. Let’s begin and tell us why do we actually want to know about prostate cancer aggressiveness? How might people use this information?

O.R.  I think it’s very important information because we now know that a substantial proportion of men over 50 do have prostate cancer foci in their prostate but most of the time they are very quiescent prostate foci and they won’t develop and won’t be harmful to the patient during his lifetime. There is an issue of over diagnosis of this quiescent prostate cancer foci. We want to avoid (inaudible) to create anxiety in the patients and sometimes in the doctors as well and not to foster overtreatment. We really need to detect aggressive cancers that might kill the patient. Actually, currently we have two different issues. First we miss some aggressive cancers and some patients are still diagnosed with clinically advanced prostate cancers and they will die of this cancer. At the same time, we detect too many quiescent prostate cancers and we run the risk of overtreatment.

H.Y.K.  I’m here now with Dr. Sung Yoon Park, a clinical Assistant Professor at Yonsei University College of Medicine in the Department of Radiology in Seoul, Korea. Welcome Dr. Park.

Sung Yoon Park, MD, PhD  Nice to see you Dr. Kressel.

H.Y.K.  It’s a pleasure. Dr. Park and his colleagues authored a provocative paper entitled “Prostate cancer: PI-RADS Version 2 Helps Preoperatively Predict Clinically Significant Cancers.” I think our readers will find this a very interesting study to read. Dr. Park why do we want to know about prostate cancer aggressiveness?

S.Y.P.  Many studies reported that (inaudible) tumor are inversely correlated with Gleason score of cancer. The cancer shows more darkness. The pathology research becomes poorer. My department MRI including DWI may predict the aggressiveness of prostate cancer before surgery or even before biopsy. In PI-RADS version 2, diffusion-weighted imaging plays a major role in the image interpretation. PI-RADS version 2 may be associated with the cancer aggressiveness I think.

H.Y.K.  How can this be useful clinically if you have an understanding of how aggressive it is, how can you use the information in clinical management?

S.Y.P.  The MR parameters such as (inaudible) or PI-RADS score can play a role for the prediction of a Gleason score upgrading or downgrading before confirmation. Radiologists can advise the possible histologic nature before surgery.

H.Y.K.  I see. In your study you developed a model to evaluate cancer aggressiveness based on quantitative parameters derived from an analysis of the MR images. Others and we’ll be speaking with Dr. Park and colleagues from Korea who have looked at more qualitative criteria, in Dr. Park’s case using PI-RADS. What was the thinking? Why did you choose to develop a model based on the quantitative parameters?

O.R.  It’s because multiparametric MRI has done a lot of progress during the last ten years, but there is still at least one issue or two problems that are linked together. Multiparametric MRI is difficult to interpret and there
is an issue of inter-reader viability and it’s sometimes a criticism from our colleagues, urologists that say well prostate MRI it works when it is done in expert centers, but it’s less performance when it is done by a regular radiologist.

**H.Y.K.** A quantitative model would reduce some of the variability and make the results more generalized, that’s the idea.

**O.R.** Yes.

**H.Y.K.** I see. Dr. Park in your study you looked at the qualitative parameters as they are listed in PI-RADS 2 to determine aggressiveness, while other groups are trying to use more quantitative methods actually calculating the ADC or other ADC parameters or looking at specific enhancement quantitative metrics. What are the benefits of using PI-RADS 2? Why do you think this might be a good way to look at this issue?

**S.Y.P.** First of all I’d like to say that I’m a user of PI-RADS because I’m not a member of a PI-RADS working group. My opinion about PI-RADS may be somewhat different from that of working group. PI-RADS stands for the Prostate Imaging Reporting and Data System, so it was designed to promote international standardization of imaging interpretation. However, technically PI-RADS scoring is based on only visual analysis for each T2 diffusion and DCE MRI. I think this revision, the proposal of this revision, was to simplify the scoring so our reach can more spread the utilization of a scoring system compared to previous version.

**H.Y.K.** I understand. The simplicity of PI-RADS may make it possible for it to be used more broadly and so to have more uniformity in terms of the determination and the criteria for aggressiveness. Thank you. You began with a lot of parameters and how did you choose the ones to include in the model?

**O.R.** We wanted to use very simple quantitative parameters so that they could be used with regular software available for all radiologists. That was the main idea. That’s why, for example, we did not use K-trans or K-ep parameters, but we used much simpler parameters for dynamic contrast enhancements and regimen such as the wash-in rate, washout rate over time to peak which was very basic parameters. The only parameter that is a bit more difficult to calculate is the tenth percentile of the apparent diffusion coefficient, but it has produced so good results in other studies that we felt it was important to include it.

**H.Y.K.** So that’s looking at the ten percent with the lowest ADC?

**O.R.** Yes well when you define the region of interest and you have a distribution of the ADC values among voxels and then you choose the tenth percentile.

**H.Y.K.** Okay. The bottom tenth percentile?

**O.R.** Yes, the bottom tenth yes.

**H.Y.K.** Okay. Now the other thing that I found very interesting in your study is that you actually included patients examined on two different MR systems and compared the results per system. Why did you choose to do that?

**O.R.** Because when you choose to go to the quantification way it’s the hard way especially with MRI because we know that it’s difficult to define thresholds that could be reproducible from one manufacturer to another; and sometimes from one scanner to another within the same manufacturer. There’s always a feeling that we might not be able to develop the reproducible model. We wanted to see if we could develop an accurate model, but also immediately if this model could be reasonably reproducible from one manufacturer to another otherwise it’s worthless.

**H.Y.K.** I was a little surprised that you choose not to include any clinical parameters in the model of cancer aggressiveness you developed. What was the reason for that, to make it less complex?

**O.R.** Yes. Of course it’s an interesting idea and I think it will be our next step, but as a first step we wanted to see where the quantitative parameters that could have good results and if they could be combined together and that was just our goal for the moment.

**H.Y.K.** I see. Your study design was a little bit complicated but I think people who are listening and watching the podcast would like a brief summary of what you actually did in your study.

**O.R.** Since 2008 we have started a radiology co-pathology correlation data base. All patients who agree and who are operated at our institution we take their pre-operative MRI and then the MRI is interpreted by two radiologists independently, and the two radiologists have to delineate all the focal lesions they can see in the prostate to give them a score of suspicion and the outlines as thought; and then the pathologists, we worked a lot with our pathologists to be able to match the MR sizes and the whole-mount specimens. We tried to cut the prostate every 3mm because the size thickness of MR size says its 3mm and our pathologists delineate on the whole-mounts all prostate cancer foci she can see. She gives them a separate Gleason score and then every week we meet and we correlate our results. She tells us you missed that cancer, you saw this one, or this lesion you delineate is benign. So we have a set of delineated lesions, either benign or malignant, with Gleason scores and so we use that data set to train and test our model.

**H.Y.K.** You talked about the matching and I have some experience doing this and it’s very, very tricky to get them...
to match even the angle of the imaging and the angle of section have to be matched, but even after that, since they're actually showing different things, the visible lesion on a T2-weighted image may not exactly correspond to the dimensions of the lesion on the ADC and that may be somewhat different than the pathology because some of these lesions are sort of infiltrative and they're not so cellular in the periphery and you don’t see the full margins. How did you try to optimize?

O.R. Yes, this is a very important question. First we took some precautions. All the pulse sequences we perform, or at least the axial images have the same center or the same number of slices so that we can have exactly the same level of image on T2-weighted imaging, diffusion-weighted imaging, and dynamic imaging first. Second, we worked with the pathologist to design a small machine to try to cut the specimen in the plane that is perpendicular to the rectal surface of the prostate and we try to line our MR slices along that plane. Then we obtain whole-mounts every three millimeters just as the MR slices. Even with all those precautions, it’s difficult to correlate the whole-mount sections and the MR images. Of course it’s a limitation of the study and we try to do our best. When we correlate the two pathology co-findings we have a microscope and we have also have the PACs system where we can see the MR images and then we try to delineate what we call the ground truth to match as closely as possible the extension of the cancer foci.

H.Y.K. So the method is nicely delineated in your paper in Figure 1. It very nicely describes that. I thought that part it is a problem and you did about as well as you can do. What did you find? What were the key findings of your study?

O.R. First we chose to try to diagnose only cancers with a Gleason score of 7 or more because they are not a lot of data showing that specific mortality due to Gleason 6 cancers is very low. I'm pretty sure that in the future we will focus more and more on aggressive cancers and probably Gleason 7 and more cancers. Second, because we were trying to detect aggressive cancers, we focused on sensitivity. So we selected the parameters or we evaluated the parameters based on their specificity at a threshold of 95% sensitivity. By doing so we had two data sets; one from one manufacturer and another one from a second manufacturer. On the first data set we evaluated our 11 quantitative parameters and the best one was the 10th percentile of ADC. And then we eliminated all the parameters that are correlated with this one and tried to find the second best, and the second best was time to peak. My big surprise was that when we did the same thing on the second data set from a second manufacturer we found the same thing.

H.Y.K. Happily!

O.R. I was ready to bet that it would be very different and we found the same order of parameters, so there might be something interesting here. Then we cross-validated models, there was one model that learned to detect Gleason 7 or more cancers on the first data set and then we tested it on the second data set and vice-versa. Here also I was very surprised that the results were very stable depending on when the data set had been trained on one data set or the other and the results were very stable. I thought it would be much more valuable so I think it might be something interesting to further investigate.

H.Y.K. How accurate was the optimized model? What was, I think you looked at the area under the ROC curve.

O.R. Yes but one must always be cautious with the AUC values because they heavily depend on the population. Obviously, the one data set was easier than the other one so the same model had better results on the first data set, data set A in the paper, and then on the second one, data set B. The results were between I think .84 to .90. The most important finding is not the AUC value in itself; it’s the fact that it does not change a lot when you use a model that has been trained on the other data set.

H.Y.K. Sure. That’s very, very, very promising. You alluded to some but what do you think were the key limitations of the study?

O.R. I always say that the important thing in the study, the three important things are population, population, and population. Yes, first we studied a population of patients who underwent radical prostatectomy because we wanted to have a very strong gold standard, histological gold standard. Of course it is a biased population and it will be more and more in the future because we operate less and less patients with, for example, with Gleason 6 cancers. Our model adds very good results in this population but I think now it should be tested in its target population which is the population of patients who are a candidate to a prostate biopsy. We’ll see, maybe the results won’t be good. We’ll see.

H.Y.K. Well then you have a confounded problem because you have the sampling error in the biopsy.

O.R. Exactly there is no perfect design and I think we should do both and then see what the results are.

H.Y.K. Hopefully you’ll have a group that goes on and you can kind of look at the relationship of the directed needle biopsies to the whole-mount and that will give you a good goal. At first glance, and we’ll be speaking with Dr. Park, the results are quite good but they’re similar, a bit better than using PI-RADS alone. Do you still believe that a quantitative approach will be the way to go with this?

O.R. I think we should go both ways. We have a problem with MRI, its lack of specificity. There are a lot of
focal lesions you can see in the prostate and a substantial proportion of these lesions are benign. There are two recent papers published, one in *Radiology* and another one in the *Journal of Urology*, but showed that with PI-RADS scores first the inter-reader agreement is not so good, it's moderate at best; and second, in the categories of score three out of five or even four out of five, proportion of benign lesions is quite high. Probably we can do better with qualitative scores and I think we'll have to work on what MR features that are meaningful to distinguish benign from malignant lesions. I think it's also interesting to work on the quantitative work because if it works it might not work due to problems with viability among manufacturers, but if it works then it will be much more easier for our regular radiologists to provide good diagnosis.

**H.Y.K.** Having looked at this in a number of areas, my sense is that the variability from manufacturer to manufacturer on ADC values it's all decreasing as we go forward so I think your approach is definitely promising. Let's turn to your study, you included some clinical parameters in your study as part of a – you did a univariate and a multivariate analysis, how did you choose the clinical parameters that you used?

**S.Y.P.** Because those clinical parameters such as PSA, biopsy information were established to assess the cancer risk such as Gleason score or a list of having lymph node metastasis or even for a bio-chemical recurrence. We wanted to compare the diagnostic performance of those well-known parameters in comparison with PI-RADS version 2 score.

**H.Y.K.** Thank you. Now for those who haven't yet read the study, can you briefly summarize what you did in your study?

**S.Y.P.** Yes. Our study design was (inaudible.) We retrospectively analyzed whether or not PI-RADS version 2 is really helpful for the detection of a significant cancer. We evaluated about 400 patients with prostate cancer who underwent MRI and surgery. The reference standard was Epstein criteria from the evaluation of a surgical specimen. Two independent radiologists analyzed the MR images. Of a cut-off score of 4 or greater was consistently found for two different radiologists and the AUC of PI-RADS version 2 score was about 0.8. I think it is an acceptable level. And sensitivity and specificity were about 77% and 72% respectively and the multivariate analysis including PI-RADS and (inaudible) parameters revealed that PI-RADS score was independently associated with the presence of a significant cancer. Finally, the imaging interpretation was reproducible between two different readers so we concluded that PI-RADS version 2 may be useful for the detection of a significant cancer. However, I think it is still unclear if PI-RADS version 2 is also able to provide a similar diagnostic performance in the pre-biopsy setting because we only analyze the surgical cases.

**H.Y.K.** I see. Just to review, the Epstein criteria for clinically significant cancer is a lesion greater than 0.5 cm and a Gleason of 7 or greater. Is that correct?

**S.Y.P.** Yes.

**H.Y.K.** Okay. The issue that you raised and you raise this in your manuscript, the study limitation of using a population going to surgery, you had a very heavily weighted sample with I think about 90% of the specimens had clinically significant cancer which makes sense, they went to surgery. Do you have any experience trying to do this in the biopsy setting?

**S.Y.P.** Of a pre-biopsy setting?

**H.Y.K.** Yeah.

**S.Y.P.** I have no experience about that but many previous studies have shown promising data about role of pre-biopsy MRI. In those research the pre-biopsy MRI can help reduce the number of a biopsy core which allow the comparable diagnostic performance for the detection of a significant cancer compared with (inaudible) assisted biopsy.

**H.Y.K.** What are the next steps for your group with this research? What are the next few things you're going to be working on?

**O.R.** We are going to test these models on the population of patients who are candidates to a prostate biopsy and compare the results of what has been predicted by the model and the results of targeted biopsies. There's also another limitation of the study. I think it's important people who are listening are aware of, is that when we delineated the “ground truth” region of interest we included prostate areas that are normal for the naked eye. If I was a radiologist at the scanner I would not delineate the region of interest that way, I would have focused it on what I see. What we are going to try is a different population and a different way of delineating region of interest but just focusing on what we see and see if the model is still working.

**H.Y.K.** So the delineation was driven by the pathology findings rather than the imaging.

**O.R.** Yes.

**H.Y.K.** And then you took all of the voxels in the path to find a region of interest and so obviously there is, depending on how great that can be, and sometimes in my experience it can be quite large actually the areas that are not visible contain cancer. Clearly that could affect the results. Now going forward what are the next steps in this line of research by your group?

**S.Y.P.** Actually in our study the reproducibility between two independent readers was somewhat high compared to the way (inaudible) another study. In a recent study
a recent article that Dr. Rosencrantz commented a very important point about the inconsistent interreader agreement among the recent studies. A radiologist at a single institution may be familiar with local imaging protocol which condition may be related with high interreader agreement. We are investigating for the improvement of interreader agreement in the interpretation of PI-RADS version 2 now-a-days.

H.Y.K. Are you trying to look at reading the same cases with radiologists from different institutions? Is that what your plan is?

S.Y.P. Unfortunately, this current study was performed in our institution, but we added the quantitative analysis into current visual analysis system of PI-RADS version 2. I hope I will share our data in coming RSNA.

H.Y.K. Oh good, okay, well I look forward to hearing it. I note you said that this was an ongoing effort at your institution. Are you in any way using this model clinically? Are you making the results available?

O.R. No not yet because we...

H.Y.K. It’s all under wraps.

O.R. Yes.

H.Y.K. Keep it hush-hush.

O.R. We wanted to make sure it is worth being used in routine practice before we can use it.

H.Y.K. That makes a lot of sense. Professor Rouviere it’s been a pleasure speaking with you and I look forward to further developments on this very exciting avenue of work. In the bone radiology when we learn about focal lesions we always used to be taught about leave me alone lesions. Lesions that you shouldn’t bother with, well maybe in the future we’ll have prostate leave me alone lesions.

O.R. Exactly, yes. I think it’s where the future is.


O.R. Bye.

H.Y.K. Are you using PI-RADS 2 regularly in the clinical management of patients at your institution currently?

S.Y.P. Actually the reporting PI-RAD score is not the obligation yet in our institution because evidences are insufficient if PI-RADS work is indeed the cornerstone for planning treatment strategy. More evidences are required to utilize PI-RADS version 2 in daily practice such as BI-RADS for breast cancer or post (inaudible) lesion.

H.Y.K. Very good. Dr. Park I want to thank you very much for joining us. I enjoyed reading the article and I certainly enjoyed your discussion and learning more about your approach to this question. Thank you very much.

S.Y.P. Thank you for the invitation.

Radiologic Analysis Demonstrates Associations between 18F-Fluoro-2-Deoxyglucose PET, Prognosis, and Epithelial-Mesenchymal Transition in Non-Small Cell Lung Cancer

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Alexander A. Bankier, MD, PhD Good morning. My name is Alex Bankier. I’m Deputy Editor for Thoracic Imaging of the journal Radiology. Our guest today is Dr. Michael Kuo from the Department of Radiology and the Department of Bioengineering from the University of California, Los Angeles. We will be discussing his upcoming article, “Radiogenomic Analysis Reveals Associations between FDG PET, Prognosis, and Epithelial-Mesenchymal Transition in Non-Small Cell Lung Cancers.” Hello Dr. Kuo.

Michael D. Kuo, MD Hello.

A.A.B. Before we go into the specifics of your article, I would like to ask you could you briefly explain to our listeners what the radiogenomics signature is.

M.D.K. Sure, so briefly one of the concepts or goals behind radiogenomics is to provide multi-scale phenotypic integration of data from macroscopic imaging such as CT, PET, or MRI and then to be able to link it to subsequent layers of biology such as tissues to pathology, cellular and ultimately genomic data. In doing that process when we link it to for example the genomics, there are many genes that are on or off in a given phenotype. What we do is we find a relationship between a group of genes that are moving in different directions and that are strongly associated or correlated with the particular phenotype that we see in imaging and that’s what we call the radiogenomic signature. It’s that relationship between the imaging phenotype and the expression patterns of the group of genes that are highly correlated with that phenotype on images.

A.A.B. I see. In your current paper you indeed describe such a relationship. You found that the radiogenomic signature of the lesions you investigated was associated with an epithelial-mesenchymal transition and this was significantly associated with drug resistance and other impor-
M.D.K. Sure so there’s a whole body of work behind the science of epithelial-mesenchymal transition. A lot of fascinating basic science and translation now moving towards drugs that try and modulate that, particularly in cancer, but a very brief summary is that it’s a conserved cellular developmental pattern that is involved in tissue morphogenesis during embryological development. There are different types. It can be activated for example in addition to during normal development, it can be activated during wound healing; and a lot of the interesting cancer is that it seems that this process is “hijacked” or reactivated in certain tumor types, certain epithelial tumor types, that give it a very – if tumors undergo this transition from the epithelial state to a more mesenchymal or differentiated state they acquire certain phenotypic characteristics that include things for example at a phenotypic level increased mobility or invasiveness; such would be like consistent with metastases, poor prognosis, and increased propensity towards drug resistance.

A.A.B. I understand you investigated these lesions in non-small cell lung cancer, but these EMT type of category also occurs in other lesions than lung cancer, in other cancers, correct?

M.D.K. Correct. It has been increasingly been found to be involved in a number of different tumor types, solid tumor types, so it seems to be an important phenotype that’s related to stem cell biology, cancer stem cell biology, and seems to be relatively pervasive.

A.A.B. Dr. Kuo in your manuscript there is a remarkable figure, it’s Figure No. 2, that shows on one hand the outcome of your study the main result, and on the other hand the complexity of the information you are analyzing. Could you briefly comment on this figure?

M.D.K. As you recall from the paper basically the goal was we had this hypothesis that the clinical features that we know are associated with high SUV such as metastases, propensity toward metastases, poor response to drugs or chemotherapy, and poor prognosis also seemed to be mirrored in tumors that are associated with post-EMT like phenotype which are similarly have poor outcome, increased metastatic potential, and chemoresistance. So we thought there may be a relationship so that was the purpose. And so we did in silico analysis and subsequently in vitro characterization in a controlled fashion in order to do independent analysis of those features and Figure 2 as you mentioned really summarizes the key aspects of that were it basically shows that radiogenomic signature where it relates the high and low SUV signature from PET imaging in the non-small cell lung cancer patients to the group of 14 genes that are significantly associated with that SUV signature. We can see there is a group that’s activated and a group that’s what we would call repressed and that if you then look at the clinical outcomes because that’s one of the key issues is that we see that indeed this holds true and the group that has more post EMT like phenotypes or activation of the signature does worse in terms of overall survival and disease-specific survival compared to the group that is low SUV and have the pre-EMT gene expression signature. So that’s basically relating the complexity of how the genes are being expressed with the associated PET imaging findings to the difference in survival.

A.A.B. Your results nicely show that the higher SUVs are clearly associated to this sub-type. Is the reverse also true? Will lower SUV be associated with a better outcome and a more favorable patient prognosis?

M.D.K. Yes. Tumors that have the lower expression are basically, if you can look at as spectrum, either you’re pre EMT or more differentiated more epithelial like tumors or you are more de-differentiated post EMT tumors. If you have the signature that’s associated with a more post EMT, undifferentiated signature, you have a worse outcome. Your overall survival is worse. Your disease specific survival is worse. Whereas if you have the other signature, so it’s a binary decision, you’re either one or the other. If you have the other signature, then it’s associated with more differentiated, less aggressive, cancer phenotype.

A.A.B. I see. At the current point do these findings have any clinical application or is this more in the realm of designing new cancer medications and so forth?

M.D.K. Well I think it could have definite clinical implications. I think you know our goal was to explore this hypothesis and to verify it at multiple levels, to drive this hypothesis and validate it independently in silico and then derive a cell-based model where we can rigorously in a controlled fashion test independently each characteristic. I think that basically there’s a lot of interest in stem cell like behavior with tumors and I think that what this can basically show is that these tumors can kind of connect the dots to some degree and that these tumors that we know that are poor prognosis that have high SUV, we can now begin to drive down and say well it may be because they’re associated with this aggressive cancer biology and we’re beginning to understand that biology and so now you know as these drugs begin to develop in the clinic, this potentially could serve as a starting point for a biomarker to be able to say, these tumors are more post-EMT like based on their imaging and so therefore they may be better candidates for these drugs for example or we could say that these patients just from a prognostic perspective we know that evidence suggests that these patients may have a more aggressive natural history so we need to be more aggressive than we would otherwise because they display these characteristics. So I think it has potential with further work to potentially have both predictive and prognostic benefits, but I think clearly more work is done and it’s a starting point.
A.A.B. I see. On more general terms you mentioned there is a big amount interest in radiogenomics. Radiogenomics certainly is one of the quickly growing fields in radiology. If a young academic radiologist at the current time point would be interested to develop a career in radiogenomics, what would you suggest to this individual? What must she or he learn and what are the skill set that this person would need to acquire?

M.D.K. I think there’s a lot of different levels in which radiogenomics entails and I think that it sits at the intersection of a number of different disciplines. For example, at the beginning of the pipeline is image feature analysis, quantitative image feature extraction, imaging phenotype characterization. Then there is the biology, the genomics or the cellular characterization, and then there’s the integration and relationship to clinically relevant end points. Ultimately at one level you have a biomarker. It’s not expected that someone can be an expert on all those things. There’s too much information. I think, at least with my students, I think it’s just — I think the key thing is just to come in with an open mind and just not to be intimidated but just to step in and become engaged and find good mentorship. That’s always key with anything and be open to hypothesis driven science and you’re going to learn. It’s like anything, it’s an apprenticeship. You learn as you work through the problems. I think that to some people it may sound intimidating because they hear the words genomics or the bioinformatics, and so a lot of people tend to shy and shift strictly towards the imaging side. I don’t think that is necessarily the case and I think it’s just something you have to become engaged in and you will learn with the process of time.

A.A.B. Dr. Kuo, thank you very much. We’re looking forward to a lot of new work from your group and thank you very much for discussing your paper with us. Good bye.

M.D.K. Thank you. It was a pleasure and thank you for having me.