Herbert Y. Kressel, MD  Hi. This is Herb Kressel and welcome to the December 2015 Radiology podcast. We have a very full lineup for this month’s podcast. First, I’ll be speaking with the authors of a controversies in radiology pairing that we’re featuring on contrast induced nephropathy. There’s been a lot of controversy about whether or not the entity exists and what the risks are. I’ll be speaking with Drs. Ulf Nyman and Jonas Björk from Malmö, Sweden and Lund, Sweden; as well as Dr. Robert McDonald and Matthew Davenport. Dr. McDonald is from the Mayo Clinic and Dr. Matthew Davenport is from the University of Michigan. I think you’ll find this discussion quite illuminating. Next, my colleague Dave Kallmes, our Deputy Editor for Neuroradiology, will be speaking with Jody Tanabe on a very provocative study on Sex Differences in Gray Matter Changes and Brain Behavior Relationships in Substance Dependence. I think you’ll find this a very stimulating discussion. And finally, Dr. Alex Bankier, our Deputy Editor for Thoracic Imaging, will be speaking with Drs. Miranda Kirby and Grace Parraga on their manuscript, Do Imaging Measurements of Emphysema and Airways Disease Explain Symptoms and Exercise Capacity in Mild to Moderate Chronic Obstructive Pulmonary Disease? This is a rather long podcast for the end of the year. So take it in small bits. Thank you very much and have a Happy New Year.

Jonas Björk, MD  Thank you.

Ulf Nyman, MD, PhD  Thank you.

H.Y.K.  Nice to have you with us. Just to sort of set the discussion, our readers may recall several years ago a provocative article authored by Dr. Jeff Newhouse, that questioned the existence of contrast induced nephropathy. The core observation, as I remember it, that Dr. Newhouse made was that although we have kind of an entire literature about contrast induced nephropathy, most of the studies that drove the concept of this entity were not controlled retrospective studies, and in the absence of a control in in-patients who are sick and tend to have alterations in renal function while they are in the hospital, he questioned whether or not contrast induced nephropathy exists. Then a couple of years ago, the group at Mayo and at the University of Michigan, Drs. Davenport and McDonald and your colleagues, reported on very large, retrospective, propensity matched cohorts of in-patients undergoing CT with and without contrast; and both of these studies, which certainly got a lot of attention in the radiology world, showed that the risk of contrast induced nephropathy using the newer low osmolar and isoosmolar agents was lower than previously thought and perhaps in the case of the Mayo study non-existent. So that’s the world as we knew it, and then Drs. Nyman, Aspelin and colleagues wrote a very thought provoking essay which we are publishing this month and they sort of questioned whether the conclusions based on the two studies may be overstated, and in fact that contrast induced nephropathy is a real item or certainly...
we haven’t excluded it. It is something that we ought to be concerned about. And they identified a number of key areas and we’ll be discussing them individually. The first area of concern was the use of relative versus absolute glomerular filtration rate as a way of stratifying the patient population and also in general the use of serum creatinine as the measure of damage in these patients. Dr. Nyman, do you want to comment on this?

U.N. Yes. Briefly, the relevant GFR is generally used in cardiology and radiology papers when estimating GFR when you’re doing contrast examination. Fundamentally this is wrong because when you are evaluating toxicity of drugs that are excreted through the kidneys, then you should use the individual's GFR. These are called absolute GFR and not the one that is adjusted to the certain or the surface area. The counterpoint that Davenport/ McDonald did, we are not sure if they really, if they misunderstood a bit of what we were writing. What we want to make clear is that we didn’t mean to use any measured absolute GFR, we meant to use estimated GFR and when you’re using (inaudible) or the (inaudible) equation to estimate GFR, then you have to recalculate the absolute values using body weight and height and the certain body surface equation. What we tried to explain in the article is that if we have a certain relative GFR entered for example between 30 and 45, if you take those patients and calculate their absolute GFR, I mean up to one third of the men will end up in the higher GFR interval and about 10 percent of the women will end up in a lower GFR interval. So by using relative GFR, you saw the mix. It’s more women with poor renal function with large men with better renal function which may dilute the results of said.

H.Y.K. So you’re basically saying that the populations may have been somewhat skewed with individuals that were actually functioning at a higher level than the way the estimate was done? Dr. McDonald you’re sort of from a place with a lot of big, beefy guys, do you want to respond to that concern?

R.M. I’m from a place with what sort of guys?

H.Y.K. Beefy guys.

R.M. Here at Mayo we still, although we'll probably eventually adopt and EGFR model and we certainly calculate an estimated EGFR based upon the MDRD equation and obviously we can use whatever other equations we want, we still sort of derive our estimates from certain creatinine measurements in terms of that’s how here how we’re sort of risk stratifying our patients for acute kidney injury following CT contrast administration. Our lab uses the NIST standard, the traceable isotope diluted mass spec. So I’d argue our, at least our serum creatinine results, even though we can certainly talk about how serum creatinine isn’t the best biomarker in the world, at least we’re using the most rigorous example where the inter and intra laboratory variability compared to another lab that uses IDMS that’s going to be very small. Going back to this idea of absolute, I think what could happen there certainly, if we looked at our data and compared to estimated to absolute, what might happen even though our results didn’t suggest there was any, I think it will just blur the lines where that cut off between when you look at Dr. Davenport’s paper where that cut off would be in terms of where there’s an increased risk of acute kidney injury.

H.Y.K. So Dr. Davenport, do you think the difference in your studies might be due to the fact that there are thinner people in Michigan?

M.D. Having lived here for ten years, I would say that’s not possible. But I think they make a good point. I mean their point is that there are better ways to accurately evaluate someone’s GFR. I actually have no problem with that. They’re probably right. You use individualized based GFR which was actually modeled based on the patient’s individual weight and individual height; you probably would have a more accurate measure of renal function. They are probably right about that. The reason why we chose to use GFR on our paper was because that’s how risk stratification for this is basically always done. So to be more clinically relevant, that’s why we chose that.

H.Y.K. Thank you. I think that’s very helpful and Dr. Nyman I was also confused about what you meant about absolute. I thought you had to have people in a clinical research center to calculate the absolute GFR so that’s very, very helpful. Now the next thing was this issue of the use of the non-contrast enhanced CT as the comparison group and how there’s maybe a misallocation of confounders as a result of that. Dr. Björk is that something you want to talk about?

J.B. Yes I can do that. I think it’s a bit problematic from a methodological point of view, but although you’re using the propensity score of stratification which I think is a very good technique. Still you might ask the question whether you can sufficiently account for the selection of differences between the controlled group and the treatment group. So I would suggest that you could do propensities for matching within the CM group, looking at different doses and match against each other; a different approach.

H.Y.K. I think that’s a very interesting idea. My own thought about that is it obviously makes a lot of sense but if we go back to where we started from where we had this whole literature on this entity that was based on uncontrolled studies, only of patients who got ill, the question that I would have is sort of where does this kind of high level of concern derive from? The core observation where at least is flawed as what we’re dealing with now with much more refinement. I don’t know if you’d like to sort of respond to that.

J.B. From my perspective, it’s not either or, you can do
both because I mean there is still this risk for a severe selection bias in the results, and one way of looking at that from a different angle was this suggestion I would say.

**H.Y.K.** I think it’s kind of a, in my own mind, sort of this discussion is very, very helpful because it’s kind of more the where do we go from here I think in doing the best for our patients. Dr. Davenport do you have any thoughts about sort of the comparison group and the problems of using the non-contrast enhanced CT?

**M.D.** Yeah I mean I actually share his concerns. When we did this analysis I thought to myself repeatedly throughout the process, is this good enough. Of course at the time, this is now 2013; it feels like it’s a long time ago.

**H.Y.K.** You’re a very young man if you think that’s a long time ago.

**M.D.** At the time, none of these studies were controlling for anything, and if they were using controls, they were simple retrospective controls with no adjustment and bias. And so to appropriately select a group that would be a suitable control, this seemed to us to be the best group at the time and then adjust for all the possible reasons renal that might predict someone would or would not get contrast. But when I read your guys’ paper suggesting to dose within a group that was a great idea I thought. I think that’s a great way to take this to the next level. Of course, at our hospital everyone was getting the same dose. So we would be unable to do that analysis. Maybe somebody else would have the data available to do it, but at the time we were not basing our dose based on that. Of course it would probably need to be in a prospective fashion because those people who are varying their dose often times are doing it on the basis of somebody’s weight and height which brings in the other issues we discussed a moment ago.

**H.Y.K.** Dr. McDonald any further thoughts on this issue?

**R.M.** Sure. I agree it is a great point on multiple levels. The first is you know is it fair to compare someone in the contrast exposed group who had a PE to someone in the naïve group who didn’t get contrast because they had some other far less severe condition but they have other co-morbidities that the propensity score matches those patients up. Fortunately when we actually drilled down to the data, it doesn’t happen that often, but it does raise a good point. There is still room for some bias in that. To sort of touch on the point in terms of varying contrast dose, our practice here does use a weight based nomogram so our dose does vary a bit with weight. Obviously we try to basically shoot for relatively similar concentrations based on body weight in adults. We actually, although we didn’t in our 2013 papers because I think I share Dr. Davenport’s sort of viewpoint, at that point we looked and we said well nobody has done anything yet so this is the first start and also I think for us it was a lot of work just to get there, but subsequently we have pub-

**J.B.** Yes I could probably comment on that because I think one strength of the propensity score technique is that you can look at the subgroups and for example you can look at the group that has received contrast media despite the fact that the propensity score is saying that you in a way shouldn’t because of the risk factors that you have at the individual level. If you look at that in the original publication by McDonald and co-workers, you can actually see that with the medium of this group, there is an elevation in this sub-group. It’s only a sub-group and it’s only observation, but I think it’s still important to look at these data more carefully.

**H.Y.K.** Good. Now the next item of concern that was raised, and I think this relates to the McDonald study, was the limited attention to the results stratified on non renal risk factors.

**J.B.** We didn’t find that that was a – it didn’t seem to be an independent risk fact for, I apologize, for contrast nephropathy, but again this is a narrow window of doses. It’s not like anyone is getting triple or quadruple dose of contrast. All we’re basically doing is keeping the intravascular concentration roughly similar between someone who weighs 50 kg and someone who weighs 150 kg for example.

**H.Y.K.** Dr. McDonald what was the result? You’re leaving us hanging here when you...

**R.M.** Can we just back up? What were you seeing in our medium risk sub-group again? I’m sorry I missed that part.

**J.B.** That was in your supplementary material. For the medium risk sub-group you had stratum one, so that is the group with the lowest propensity score right?

**R.M.** Yeah.

**J.B.** You had a clear elevation there in the same risk?

**R.M.** Yeah, I see what you’re saying. Right so one of
the propensity score matching techniques we used was a stratification method which we showed the strata within each, so it's sort of like stratification of the strata, so we stratified our patients in those risk groups based upon our sort of clinical experience of how we sort of mentally triaged patients. The low risk group were patients with creatinine less than 1.5 who we really didn’t think were our great risk. Although we didn’t know, but those were the people we were least concerned about. The medium risk were between 1.5 and 2 in terms of a baseline serum creatinine and the high risk was anything about 2 and so those were the patients we were the most concerned with. And frankly for that 2013 paper, we were very interested in that medium risk group because that comprises a large percentage of our patients. The high risk group patients, even though they seem very ominous, they are a very low fraction of patients you actually scan every day. And so I remember exactly what you’re talking about, that in the stratification, it doesn’t clearly march as you normally would expect it. I remember seeing that and being a little bewildered by it as well. As to why that is, I guess for that one thing I guess I was more interested in being intellectually honest and putting our results than trying to redo it, but when we subsequently re-analyzed those data again using like a boot strapping model and this ended up being in the supplement to the paper that looked at dialysis and mortality. So we did a boot strapping model where we compared multiple different propensity score matching method and we had the computer rerun the propensity score matching 100 times for each of I believe the five different methods, we had very similar results every time and we were able to sort of narrow of confidence interval. I think the results overall still argue that, at least from a statistical point of view, we can’t discern an affect that you can call contrast induced nephropathy based upon our data, but no I acknowledge exactly what you’re talking about that the stratification was not this clear ramp up from the lowest to the highest risk based upon their propensity score.

H.Y.K. So I know that a lot of this discussion will seem very heavily in the weeds to a lot of people who are listening to this, but I must say I think it’s important because in the end we have these very complex, multi-factorial situations and we’re trying to make decisions about giving an agent to people that will affect their lives potentially. It’s not trivial and I think it highlights the importance of having good quality data and a good quality analysis and that I’m pleased to see that both Drs. Davenport and McDonald the questions aren’t over, that we’re trying to build from there. I think that was really the point from Drs. Nyman and Aspelin and Björk why you wrote that. That kind of we don’t have the final answer, there are issues that remain to be explored. On the other hand, in the practical world of clinical radiology, people need to make decisions and practice. I think one of the points of the Davenport and McDonald papers was that perhaps you’re withholding contrast from people who wouldn’t have adverse events on the basis of it and who would benefit from the added information available. So that brings me to sort of knowing what we know now, where are we? Dr. Davenport you’ve been involved I think with ACR Committee looking at contrast guidelines and perhaps you can tell us where we are, what the guidelines are, and what the changes have been.

M.D. Sure I’d be happy to. Recently the chapter on contrast induced acute kidney injury was rewritten. I think there are two major changes. One is definitional and one is based on the threshold. The definition difference now is that what was previously termed CIN, which is you get contrast and then 48 to 72 hours later you have a bump in your serum creatinine and the old definition CIN is no longer. That’s now called post contrast acute kidney injury. In other words we’re taking away the causative statement and placing it within the name and that’s now post contrast kidney injury. And CIN is now restricted to only that which can be confirmed to be directly causative from the contrast material which of course is extremely difficult to disentangle on a per patient basis and requires a randomized controlled trial or some kind of advanced retrospective statistics. The second change is based on the threshold. This caused a lot of controversy, frankly speaking, in that room as to what number should we put if anything? There was some people that said we shouldn’t even put a threshold down because we don’t know yet and you might imagine who that would have been who would have made those comments. And then there were other people who said no, we need to guide people so they what to do and after a lot of discussion we decided that the level which has the most level of evidence in the literature based on controlled studies was a number of less than 30. And we make a bunch of statements in there which is the following, one this pertains to IV media only and secondly is that anything involves a risk benefit decision. It’s more complicated than just a simple number. I can go into a long winded discussion about why we chose less than 30, but that’s what we chose.

H.Y.K. Good. Dr. Nyman how do things stand in Europe? Has there been any changes?

U.N. No there has not been any change in standard. We had a discussion in Sweden at the radiology meeting and there were people from the European Society of Radiology taking part too, and the general recommendation was to sit on your hands and wait, don’t do any changes. Basically the guidelines we have in several countries in the European society, one risk group is those with GFR below 45. Then you have the other patient group with multiple risk factors and basically independent of what the GFR is, if you have a patient with cardiac decomposition, diabetes and so on, unstable renal function, unstable hemodynamics and so on, be careful then. These are the general guidelines. But then it came into practice from my personal point of view, I seldom see any problems because you can solve a problem in a lot of different ways and I what I use very frequently in the risk categories is doing ADCT and wrapping up the mAs,
the patients are pretty old generally. You don’t have a concern about radiation and you can – basically half the contrast we can dose.

H.Y.K. So just reduce the dose if you’re concerned?

U.N. Sorry?

H.Y.K. The idea of using a lower dose and upping the mAs if you’re sort of in that borderline zone?

U.N. Exactly so you don’t get too much noise in the images but then you can almost half the contrast medium dose.

H.Y.K. Okay, going back to the US, Dr. Davenport what’s happened to practice at the University of Michigan? Are you using the current ACR guidelines or are you doing something a little different?

M.D. So we started using something very similar to the ACR guidelines prior to ACR releasing those guidelines. So what we use is, if a patient has acute kidney injury or chronic kidney disease with EGFR of less than 30, it triggers a provider to provider conversation. That’s our guideline. So we have a discussion about what to do. When the EGFR is 30 or higher than we don’t have any specific requirements.

H.Y.K. Experientially, have you had these conversations? What’s the usual outcome?

M.D. Because our policy tends to be more liberal than what the referring services believe about the nephrotoxic potential of contrast, we have these conversations infrequently because there is not many people who are asking for this. And if they’re asking for it, they know there’s a risk probably too and it’s on everybody’s radar.

H.Y.K. Good. I’ve actually kind of consulted with physicians and sort of had this discussion and we have kind of just on limited numbers, but we have been a little bit more liberal about using it if it’s really an indicated situation. Dr. McDonald, where are we at Mayo with this issue?

R.M. Right so you know our internal use we still, like I said, even though we calculate the EGFR we still are using serum creatinine right now, but it’s very similar, we have a similar policy to the ACR and to Michigan of that below a creatinine of 2 we feel it’s safe to administer contrast based upon the results from our study and Michigan study. We thought that was the most conservative approach and again it aligns nicely with ACRs guidelines because a serum creatinine of 2 is relatively close to 30. I anticipate at some point we’ll transition to EGFR based measurements and adopt a 30 threshold; and in terms of phone calls, well certainly we still get them because what our thoughts are in the department versus what providers think, clearly we certainly get phone calls where people are worried about giving contrast to someone with serum creatinine of 1.4. We certainly try to counsel them, but our policy here is to sort of ultimately the decision is with the ordering provider, so we’ll try to let them know what the best evidence is and let them make the best clinical decision from there.

H.Y.K. Well thank you. I want to thank all the participants today. I think this has been a very enlightening discussion. I think people perhaps will have a better sense of the complexity and thought process that goes into kind of thinking about these guidelines. Also from my perspective, the importance of good quality studies, we kind of throw out what we need is a prospective, randomized controlled trial, but with something like this where the incidence is relatively low, it’s very, very challenging to put these together and quite frankly in the environment that we’re in, I don’t know that we’re going to be able to see this and so we’re stuck in a situation where we kind of lurch forward using the best information and processing what we have, and we just have to be aware of the limitations of that. So I want to thank you all for participating. Thanks to our colleagues in Sweden for your contribution in the essay and also in the podcast and thanks to doctors Davenport and McDonald once again. So thank you.

Sex Differences in Gray Matter Changes and Brain-Behavior Relationships in Patients with Stimulant Dependence

Radiology 2015; 277:801–812

Michael F. Regner, MD • Manish Dalwani, MS • Dorothy Yamamoto, PhD • Robert I. Perry, MD • Joseph T. Sakai, MD • Justin M. Honce, MD • Jody Tanabe, MD

David F. Kallmes, MD Hello and welcome to this video podcast. My name is David Kallmes, I am Deputy Editor for Neuroradiology at the journal Radiology. I’m joined today by Jody Tanabe who is Professor of Radiology, Chief of Neuroradiology, and Vice Chair of Research at the University of Colorado. Welcome Dr. Tanabe.

Jody Tanabe, MD Thank you for having me.

D.F.K. Sure we’re here to discuss your really exciting paper entitled “Sex Differences in Gray Matter Changes and Brain Behavior Relationships in Substance Dependence.” First of all can you just share with us what are the known sex differences in the natural history of substance dependence?
ing several differences at every level of drug use. So for example women have been shown to escalate their use of drugs much more quickly than men. While it’s true that men compared to women tend to engage in more risky behavior such as experimenting with drugs, it turns out that women are much more likely than men for example to use drugs to reduce depression or alleviate stress and that is one of the thoughts behind the quicker downward spiral for women than men. There are also some behavioral differences for example with psycho-stimulants, women report different levels of euphoria and that is thought to be related to the menstrual phase. The good news is that women also tend to seek treatment at an earlier time point than men. A lot of the sex differences have also been substantiated by animal studies. There have been several animal studies that show that female rodents acquire self-administration paradigms much more quickly than male rodents.

D.F.K. Okay so with that background of the differences between men and women with substance dependence, what did you do in this study?

J.T. In this study, it was a cross-sectional study where we recruited about 127 individuals roughly divided between healthy controls and abstinent substance dependent individuals and we compared the gray matter volume at a whole brain level and at a regional level between patients and controls and we determined and investigated the effects of sex on those differences. There have been a number of studies that have shown that gray matter volumes differ between drug users and controls, and we also know there is sexual dimorphism just being female or male. But there have been very few studies that have looked at the interaction of these two factors. So we conducted that analysis on T1 weighted structural images and then we determined whether there were any relationships between the gray matter volume and behavioral measures that may be important in drug dependence as well as measures of drug severity itself.

D.F.K. What did you find?

J.T. So our main finding was that there was an interaction between sex and drug dependence diagnosis on gray matter volumes involving multiple areas. Primarily frontal, there’s a lot of pre-frontal ventrimea pre-frontal and the lymphics system as well as the temporal lobe. It turned out that these differences were really driven by the women. Drug dependent women had much lower gray matter volume than control women, and we did not find these substantial differences in the men. Those were our volume metric findings and then we took it further and found that there were correlations between certain behavioral metrics. So the one that is most interesting is that there was a negative correlation between the gray matter volume in the nuclei accumbens and drug severity. We measure drug severity by summing the dependence and abuse symptoms across all drugs for each individual.
study and look at how brain volume changes over the dynamic range of short term versus long term abstinence. We did not do that, but that is of course the ideal study. What we can conclude from this study is that these changes are sustained without the effect of acute drugs. On average our patients were off of drugs for about a year. That's important because, for example, we know that alcohol in the short term can have significant changes in brain volume and metabolism with acute sobriety over the course of weeks. So I think what this study demonstrates is that we can detect sustained changes. Whether it came before or after the drug, I cannot say.

D.F.K. Sure. So I note that you have a current NIH grant to study this, can you share with us what you're doing in that grant? Are you looking at other features of the disorder with other imaging techniques?

J.T. So we're currently funded to look at decision making in drug users. Specifically, we look at risky decision making and we're looking at the striatal system as well as the frontal networks in looking for neuro correlates that may underlie bad decisions made by drug users. Interestingly, our RO1 was not originally funded to look at sex effects, but this information came out afterwards.

D.F.K. Okay. Certainly drug addiction is a public health problem and congratulations on this fantastic line of research. Is there anything else you want to share with the listeners about your project or future projects?

J.T. I'm appreciative of the chance to share this information and I hope it inspires people in the radiology community to do similar sorts of work.

D.F.K. Congratulations on your paper. We greatly appreciate your support of our journal and we look forward to future great papers from your group. Thank you.

J.T. Thank you for having me.

COPD: Do Imaging Measurements of Emphysema and Airway Disease Explain Symptoms and Exercise Capacity?

Radiology 2015; 277:872–880

Miranda Kirby, PhD • Damien Pike, BSc • Don D. Sin, MD, MPH • Harvey O. Coxson, PhD • David G. McCormack, MD, FRCPC • Grace Parraga, PhD

Alexander A. Bankier, MD Hello. My name is Alex Bankier and I'm Deputy Editor of the journal Radiology in charge of Thoracic Imaging. Today with us is Dr. Miranda Kirby from the James Hogg Research Center at the University of British Columbia, and on the phone is Dr. Grace Parraga from the Imaging Research Laboratories at the Roberts Research Institute. Our podcast today is to discuss the recent article from this group. The title of this article is the question, “Do Imaging Measurements of Emphysema and Airways Disease Explain Symptoms and Exercise Capacity in Mild to Moderate Chronic Obstructive Pulmonary Disease?” Dr. Kirby, what is the answer to this question?

Miranda Kirby, MD The short answer to that question is yes. We know that exercise, capacity limitation, and symptoms are well described in all COPD subjects including mild COPD subjects, but what’s not as well known is what are the underlying determinants of the limitation and symptoms in these patients? So what we investigated, a relatively large group of these patients using hyper-polarized helium magnetic resonance imaging, and we found that it was emphysema that was actually the dominant contributor to both exercise limitation and symptoms.

A.A.B. I see. Why does helium MRI work so well in early COPD while pulmonary function tests which are considered the reference standard if you want for this disease do in fact not?

M.K. Well I think that the hyper-polarized helium MRI measurements are actually giving us functional information on a regional basis. So we’re able to visualize all of the places in the lung essentially where air are able to access, so if there are parts of the lung that there’s obstruction of the smaller airways or medium sized airways, we don’t see the gas going there. As well when we have a lot of emphysematous tissue destruction, we’re able, and as the gas is able to access those areas; we’re also able to measure those enlarged airspaces. We think that these more global pulmonary function measurements like FEB1 are maybe not as sensitive at measuring the contributions of both the smaller airways and more mild emphysema.

A.A.B. I see. Dr. Parraga, why is it so important to diagnose COPD early in the course of the disease?

Grace Parraga, MD Well I think there are two ways to look at this from our perspective, and I think mainly what we wanted to explain was why in milder disease are there such differences and why is there so much heterogeneity amongst patients. Patients tend not to be diagnosed until they have symptoms and they’re diagnosed using the standard clinical tools not imaging. So they’re diagnosed using spirometry. Even yet, in the mildest forms, we see a large heterogeneity in symptoms and exercise limitation. I think early on I think it would be important for patients to get a full workup so that the underlying contributions to their disease are well understood at the
earliest time point so that intervention can be thought through based on that information. I think the second point is that folks who are smokers or ex-smokers need to understand that these kinds of tools are out there and that the sooner they understand what’s going on in their lungs the better. And I point to other kinds of tests for heart disease, and Alzheimer’s where the paradigm for early understanding helps with treatment decisions.

A.A.B. I see. Dr. Kirby, there is a lot of talk about CT definable phenotypes of COPD. Is helium MRI looking at the same phenotypes and what is the added value that helium MR can bring to the feel of imaging in diagnosing COPD?

M.K. That’s a really great question. With CT, we’re able to quantify emphysema in all regions on the lung, where with hyper-polarized helium gas we’re only accessing those areas of the lung where gas had access. We’re also able to directly quantify the dimensions of the airways. Where with the hyper-polarized gas MRI we’re getting more of a functional measurement of which airways may be obstructed or narrowed with the gas can access. So we are really getting very complimentary information. I think that our studies and our previous studies have shown that particularly with our hyper-polarized diffusion weighted imaging we may be able to identify and measure emphysema more at the earlier stages. We’ve shown that there’s an elevated ADC values as well as normal diffusion capacity at level of carbon monoxides of DLCO values in subjects that have a normal spirometry and normal CT measurements. So it may be more suited for looking at disease in early emphysema in these more mild subjects.

A.A.B. I see. The question for Dr. Parraga, given the limitations to the availability of hyper-polarized helium and helium in general, what are the practice of clinical patients of using the method you described in COPD patients?

G.P. Well there are practical limitations for certain and this study should be taken in that context. There is likely very little translational potential for helium MRI, but I think what we’re doing now is opening up a conversation about using imaging in general in COPD patients; and I also point to the fact that while we have been using helium MRI, and this is a very large longitudinal study that started back in 2009, we’ve transitioned to helium xenon MRI, excuse me, and that’s the 129 xenon isotope and that technology is now on the verge of FDA approval and more widespread clinical use. So I think our group and most groups worldwide now have transitioned to xenon and there’s some interesting properties of the xenon gas itself that actually gives us great optimism because there is more sensitivity, xenon is more sensitive to some of these airway and parenchymal abnormalities in COPD and other obstructive lung diseases.

A.A.B. I see. So just to make it clear for our listeners, you believe that most, or a substantial part at least, of the results that were previously obtained with helium can be extrapolated into the xenon framework?

G.P. Absolutely. I think we’ve shown that and other groups have shown that and in particular in COPD and in asthma and in fact we’re very optimistic about COPD because of its sensitivity to airway obstruction. The gas is thicker and more dense and it is a better approximate or estimate of the constituents of air, the air that we breathe. So we’re very optimistic about the potential for xenon to be used clinically especially in cases where you can’t explain why the patient can’t exercise, why they’re feeling so bad, and FEB1 and other sort of clinical measurements don’t explain what’s going on with the patient.

A.A.B. Interesting. A question to both of you, in the COPD imaging with MR is always in competition with CT, with pulmonary function test, so what methods either low cost methods or very widely available methods while MR is none of the two. Where do you extrapolate a little bit into the future? Where do you see the future role of MR in the work up of COPD and let’s say in five or ten years from now, where do you see the role of MR in the clinical management of patients with COPD.

M.K. I guess I look at it as not as MR versus CT versus FEB1, I look at it as imaging versus these other cheaper more global measurements that aren’t as sensitive. So I think that first I really believe in more multi modality imaging approach because they do provide very complimentary information and I think long term I see imaging being used for more clinical phenotyping and if these COPD patients can be phenotyped early on, then treatment can be targeted towards those specific phenotypes and that can in the long term improve outcomes.

A.A.B. I see. Dr. Parraga do you want to answer that?

G.P. Yeah. I agree with Dr. Kirby. I also want to point out that I acknowledge that we’re living in a constrained health care economic system and that in some cities and some sectors, access to MR and CT may be limited, but again there is an economic argument for phenotyping patients and having a better look at what’s going on with patients, because COPD costs a lot of money to the healthcare systems independent of how you’re paying for it and what we’ve tried to do is show the utility of imaging to save costs. For example, to save costs if you understand what’s going on better, you might obviate the necessity of hospitalization for exacerbation. You might be able to treat earlier and better so that the patient is more functional and feels better, and then they can more readily differentiate when their symptoms are just day-to-day problems or they’re in fact experiencing an exacerbation and need immediate care. We’ve looked at the health economic framework for our health care system which is a little bit different than the U.S. and I think that on the whole if you can make a commitment to scanning specific patient populations as quickly as possible, an MR and CT for a patient can be completed in about ten min-
utes, then there’s a good argument for using it on the economic and on the patient and the patient treatment basis.

A.A.B. If I understand your message right, you’re making a point for potentially investing more in the diagnosis in early stages of the disease in order to make economy to spend less in later stages of the disease, correct?

G.P. That’s correct and perhaps there’s an argument for even every two years doing follow-up on the patients to watch the pathologies as they progress. The cost of a scan every two years far outweighed by the cost of all the other types of interventions that happen in these patients. On that basis alone I think it’s justified that we continue to develop these tools.

A.A.B. I see. I think this is a very interesting perspective and a very interesting note and look out into the future to end our conversation. Dr. Kirby, Dr. Parraga, thank you very much for being with us.