my review of literature was whether there were any specific concerns in cardiology patients with F-18 FDG.

In my review, the only thing that I noted was not a direct result of F-18 FDG, per se, but rather it was in a sense a by-product of the way the drug is used. Sometimes it is administered in cardiology after a glucose bolus, in other times it is administered under fasting conditions. And in those situations, patients with impaired glucose homeostasis may have some additional safety concerns.

The criteria that we used were very similar to the criteria that Dr. Houn used in her review for oncologic indications. I won't go through and reiterate them all, I will just cite some of the additional things. Particularly for the cardiac indications, there were references in the American College of Cardiology, and the American Heart Association Guidelines, and the United States Pharmacopeia Drug Information book that were also culled. These are the number of references that we received. In addition, we also receive a number of references from the PET community.

I took a similar approach to Dr. Houn in terms of my review, although the way I say things might be somewhat different. The framework for the literature review was in part based on many of the concepts that are delineated in the Draft Guidance for Industry on

"Developing "Medical Imaging Drugs and Biologics." This shows where you can find it on the Internet.

In terms of several claims, when I did my review of the literature I made a quick assessment of whether I thought the evidence supported a claim of diagnostic or therapeutic patient management, which generally requires a very high standard of evidence and data to support and oftentimes requires randomized prospective clinical trials. In my review of the literature, I didn't really find adequate evidence to support a diagnostic or therapeutic management claim, per se.

So if you asked me where would I classify the claim that I've had proposed, I would say it is probably a mix, as Dr. Tulchinsky has indicated. Sometimes these things don't fit necessarily into just one category. I would say there are functional physiological or biochemical components to it, but I would also say that there are disease detection assessment components to it as well. In fact, you might also argue that it is under "Other" because it provides prognostic information about the functional status of myocardium.

So what I looked for was whether the information would be clinically useful, whether the information in the papers was valid, and whether the

product was studied in a defined clinical setting. And I won't go into these in detail because Dr. Houn has already addressed many of these. But I will comment on them throughout my talk this morning.

By way of introduction, what I would like to do is, for those of you who are not cardiologists, talk about myocardium. Myocardium when it is dysfunctional sometimes that dysfunction is reversible and other times it is not reversible. A classic case of nonreversible myocardial dysfunction is when there is a myocardial infarct and the heart is irreparably damaged. However, in the cardiology literature there are two main categories of reversible myocardial dysfunction that are often described. One is myocardial hibernation, and I'll talk about that a little bit, that will be the bulk of my talk, and that is basically reversible myocardial dysfunction in patients with coronary artery disease. So what myocardial hibernation is is chronic reversible left ventricular dysfunction due to coronary artery disease. In contrast, myocardial stunning is also myocardial dysfunction but it oftentimes results from an acute post-ischemic insult to the heart.

And just for purposes of my presentation in terms of clarifying my terminology, I'll use the terms hibernation and viability interchangeably even though there

may be shades of difference in the way that the terms may be actually used. In my view, the data support a claim for myocardial hibernation because hibernation implies a reversible state of myocardial dysfunction, whereas viability doesn't address the functional state of the myocardium, per se.

And similarly, I will use the terms radionuclide uptake, radionuclide localization, and radionuclide accumulation to mean the same thing. Most people in terms of jargon use the term uptake, although as we have heard from Dr. Laniyonu, FDG trapping is not only a result of glucose uptake into the cell but it is also a consequence of a phosphorylation and limited dephosphorylation. However, in the literature oftentimes people refer to uptake. Whereas, for the purposes of my discussion, I'm just using those terms interchangeably.

Just a brief summary. As Dr. Laniyonu said, F-18 FDG is taken up into the myocytes by the glucose transporter after phosphorylation by hexokinase, it is not metabolized further. And so phosphorylated F-18 FDG accumulates in the cell and generates a signal.

Also as alluded to by Dr. Laniyonu, most of the literature that I reviewed referred to the use of FDG in combination with perfusion assessment. There are two basic patterns that are referred to. One is flow metabolism

mismatch, which is defined as increased accumulation of FDG compared to myocardial perfusion. And that in the literature is thought to be reflective of hibernating tissue. So, in other word, it is a hot spot in terms of the FDG compared to a cold perfusion spot. And then on the alternative is the flow-metabolism match, which is concordant reduction in both F-18 FDG and in perfusion. So, in other words, there is a decrease or a cold spot for FDG as well as for perfusion.

One of the main criteria that I used, and I think it is different from some of the other applications that will be discussed or some of the other products that will be discussed, is that in my literature review the performance of FDG was not being compared to another product, or to a gold standard, or to pathology, or something like that. But, rather, the results were compared to the functional outcome of the particular myocardial segment after revascularization.

So, in other words, prior to revascularization, segments that were dysfunctional or that were asynergic were identified and then, after coronary revascularization either by CABG or through angioplasty, those same segments were re-evaluated to see if their function came back. Whether or not that function came back in my review was the ultimate arbiter of what truth was or the true state of

that myocardial segment, whether it was actually hibernating or not.

I have ten studies I've summarized in my review, and in this talk they are all basically of the identical core design, which I would like to emphasize because, once we've walked through this prototype, all ten studies basically fit the same prototype. And so that things don't get tedious, I will try to emphasize different things during each of the studies. But let me just walk through the prototype so that people have an understanding of what the clinical trial design was for each of the studies that I reviewed.

Basically, the studies enrolled patients who were planning to go to coronary revascularization either with coronary artery bypass or with angioplasty. And in those patients, those patients had some sort of evaluation at baseline or prior to revascularization of their myocardial dysfunction. Whether it was echocardiography, whether it was radionuclide ventriculography, or whether it was contrast ventriculography, it was not really particularly deemed to be relevant because each of those methods are sufficiently reliable and valid as methods to assess ventricular segmental motion. So at baseline, asynergic myocardial segments were identified.

And then the degree of severity of the

dysfunction was ranked. And usually this was done in almost all the studies on an ordinal scale, where, for example, one might be normal motion, slightly worse than normal motion might be hypokinesis, slightly worse than that may be akinesis, and then actual dyskinesis where the segment is moving in the wrong direction would be worse than that, and some studies even extended the scale by various ways, such as including aneurysms or breaking hypokinesis into mildly hypokinetic or severely hypokinetic. But the bottom line is that wall-motion was assessed the same way by the ordinal scales in virtually all the studies, with one perhaps or two exceptions.

Prior to revascularizations, these patients then usually had an assessment of perfusion. Now whether it was perfusion that was assessed by PET with ammonia, or PET with rubidium, or whether it was some other marker of perfusion, like Thallium, again, in my review was not deemed to be a significant variable. These methods are sufficiently reliable and valid for evaluating perfusion.

And then there was some sort of assessment with F-18 FDG in terms of predicting viability. Subsequently those patients underwent coronary revascularization. And then after revascularization, the true state of those myocardial segments was then assessed. And usually that was by the same technology, either echocardiography or

contrast or radionuclide ventriculography that was used to assess the state of that segment at baseline or prior to revascularization.

And if you have looked through my review, you will see that I spent a fair amount of time talking about what happened to patients, and who was included, who was excluded, whether the segments were included or excluded because I feel that's an important way in which a study can be biased. If only the most representative patients or most representatives segments are selected, then that can give different assessments of performance measures like sensitivity and specificity than they might get if all those patients were included.

Performance measures like sensitivity, specificity, and negative and positive predictive value were calculated by the usual formulas. Since the studies were small, I want to emphasize some caveats about the calculations and the performance measures that are reproduced in my review and on some of these slides.

First of all, many of these studies had other principal objectives than what I was actually at them for. If you looked at my review, sometimes the review doesn't look very much similar to what the actual paper was. And so, in a sense, this could be viewed almost like a retrospective analysis of the literature.

Also, performance measures like sensitivity, specificity, positive/negative predictive values were derived from relatively small number of patients. So you will see in the confidence intervals that some of them are fairly wide because the number of segments or the number of patients that were included were relatively few.

Furthermore, there was no standard definition of what a myocardial segment is. It was at the discretion of the investigator. Some studies divided the heart up into three or five segments, others divided it up into many, many more. And so it was simply a question of how the investigator chose to conduct his or her study in terms of defining how many segments there were per any given left ventricle. And so, particularly when some of those segments may not be mutually exclusive of one another, or if they are overlapping one another, then it becomes difficult to start combining performance measures like sensitivity and specificity across studies.

And finally, as everyone knows, performance measures like positive and negative predictive value, and accuracy are highly dependent or highly influenced by the prevalence.

So some of the things that I looked for were whether there was a sufficient detail of study design, population, doses used, endpoints, image acquisition, image

interpretation, and statistical analyses. And I tried to lay that out pretty carefully in the written review. And I'll go through that fairly quickly in my talk.

I was concerned about whether there was an adequate study design, whether the study was appropriately controlled. And, again, rather than a gold standard, I was looking at a functional outcome of hibernation, whether, in reality, after revascularization that particular myocardial segment regained its function or not. A blinded image evaluation, and sufficient accounting of patients and segments. And also whether the study population was sufficiently similar to the population in which F-18 FDG is intended. And so that is why I added that slight addition to slide number 3, or as we will see it on slide number 93, that in the indication it would be worded for use in patients with coronary artery disease and chronic left ventricular dysfunction. Because the bulk of the studies that I looked at evaluated the drug in that patient population.

This is just for bookkeeping purposes. These are the ten principal studies that I found in the primary literature that supported this claim. They are listed alphabetically. And I'll go through each one of them and try to emphasize slightly different points in each one.

The first study was a study by Baer. And the

objective was to assess the predictive value of myocardial viability diagnosed by dobutamine transesophageal echocardiography compared with F-18 FDG PET for left ventricular recovery. In my review and in my talk, I won't really be talking about the results of dobutamine echocardiography because, although I think that is relevant and highly useful clinically, the issue on the table is really whether F-18 FDG, there is enough evidence and data to support its use for this purpose.

One of the criteria that I used, as similar to Dr. Houn, was whether the studies were prospective. And virtually all ten of these studies were prospective studies, and some enrolled consecutive patients, and virtually all enrolled patients with coronary artery disease and chronic LV dysfunction who were planning to go for some sort of coronary revascularization procedure.

Perfusion, interestingly, was not assessed in this study. FDG was given at a dose of 10 millicuries. Quantitative image evaluation, the heart was broken up into 28 segments, and the definition of viability I've emphasized in each of my slides, and in this particular study viability was defined as F-18 FDG accumulation of more than 50 percent of the maximum.

Patients in that study underwent either CABG or angioplasty. And then wall motion was assessed by

transesophageal echocardiography. It had blinded image evaluations by two readers on a four-point ordinal scale. So 42 patients were included in the analysis, 26 of whom had improved function. If you look on that as a segmental basis where there's 28 segments per patient, that ends up to be 1176 segments that could possibly be evaluated. And I'll talk about this in a second, but let just run through the numbers.

What this paper did is, as is typical, it restricted the evaluation to those 405 segments that were akinetic or dyskinetic at baseline or had some sort of abnormal function at baseline. In other words, normal segments were not included in the analysis; segments that had normal function at baseline were not included in the analysis. However, then there is another cut which was made, and that is that not all segments were included in the analysis that were akinetic or dyskinetic at rest. In fact, only 371 segments of the 405 that were deemed to be successfully revascularized were included in the analysis. So there's two primary levels here in which segments are not being included in the analysis. One is if they are normal at baseline, they are being excluded. And second, if the revascularization was not felt to be successful, then they were excluded. And of those 180 had improved function.

And so the diagnostic performance of FDG in this situation was calculated both by segment and by patient. And, again, I don't want to emphasize too much the particular numbers here, but the sensitivity was 93 percent, these are the 95 percent confidence intervals going from 88 to 96 percent, and for specificity, going from 59 to 72 percent.

So what were some of the strengths of this study. Consecutive patients, prospective, the wall-motion assessment was blinded. And as I pointed out in my review, there were two levels of blinding that I felt were most important for these studies and which I tried to emphasize. One is whether the wall-motion assessment, which is the outcome of interest, whether those readers were blinded to the results of FDG or not; and the other is the opposite of that, whether the interpreters of the FDG PET images were blinded to the result of wall-motion analysis.

Now, I think it is particularly important that because the wall-motion analysis in virtually all cases was a visual one, a qualitative one, on ordinal scales where investigators were trying to make a determination about whether it was hypokinetic or akinetic or dyskinetic wall-motion, that that sort of assessment be blinded. And there were multiple readers for wall-motion and they were blinded.

However, I will comment that even in a quantitative image analysis, as is done for many of the PET studies, there are reasons to think about blinding them as well. That's because even in a quantitative analysis, to the extent that there is an operator/reader interaction, or regions of interest are being drawn, or there's any sort of human interface, that's a potential for bias if the PET reader is aware of what the wall-motion analysis showed. However, in my review, I felt that that was less likely to be source of significant bias, and I thought that the wall-motion assessment was the most critical type of assessment that should be blinded.

Limitations. Not one of the studies that I reviewed had more than 50 patients that was included in the analysis. But this was one of the three largest. However, I felt that because there was sufficient similarity of the ten studies in terms of the procedures that were done and the outcomes that, in aggregate, although you can't necessarily point to one or just two, in aggregate the data were supportive of the indication that I had indicated at the outset of this talk..

The number of PET readers was not specified. And interestingly, in this study wall-motion assessment was based only on systolic wall thickening and not on wall movement.

I do want to emphasize at the outset one other thing that I didn't emphasize about this study that I thought was a real advantage, and that is that a by-patient analysis was performed. Whenever we are talking about units such as segments of a myocardium we run into the risk of that not having clinical significance to the patient. Ultimately, what is of concern is that the diagnostic modality or therapeutic modality somehow ultimately benefit the patient. And so patients are ultimately the unit of interest for all of these. And this was one of the few studies that really did a by-patient analysis. Most of the studies were limited insofar as they only did by-segment analyses.

Ideally, what you would like to see is a clear progression that regional or segmental wall-motion results in global ventricular improvement in motion or function, which results in improvement in patient symptoms or in patient survival. But most of the studies just really stopped at the level of just doing a segmental analysis. When I get to the secondary literature that I reviewed, that's where I feel that comes in. Because I think those secondary literature articles give a measure of comfort that this regional wall-motion improvement that we're seeing in these ten principal studies is being potentially translated into some sort of patient benefit in terms of

either exercise capacity, symptoms, or survival.

I'll go through these fairly quickly. They are all of a similar design. I'll just try to emphasize points that I haven't emphasized before.

Gerber. The objective was very similar here, consecutive patients with coronary artery disease. This, along with one other study, only looked at the anterior wall of the left ventricular or the distribution of left anterior descending artery. And that was the only myocardial region of interest for purposes of this study. In other words, patients were enrolled only if they had dysfunction of the anterior wall at baseline. And then, after revascularization, some sort of recovery of that anterior wall dysfunction was looked for.

Ammonia PET agent was also used to assess perfusion. And, again, there was a comparison in this study to the performance with low-dose dobutamine, in this case it was two dimensional echocardiography transthoracic as opposed to transesophageal echocardiography as in the study by Baer.

Major limitations. Doses were not specified. However, the FDG interpretation was quantitative. It involved an operator-interactive image analysis. It was limited to the anterior wall segments. And viability was basically assessed on whether there was a match/mismatch

pattern. Revascularization was performed by CABG or angioplasty, and the success of the revascularization was assessed by fairly rigors means by angiography. And wall-motion was assessed by 2-D echo on a 3-point ordinal scale.

Thirty-nine patients were included in the analysis. And accordingly, since only the anterior segment was evaluated, only 39 segments were evaluated. So in this case, there is a concordance between the by-segment analysis and the by-patient analysis. It is essentially the same thing. There were only three studies that in effect did that; the one I just mentioned by Baer, this study by Gerber, and another study that also limited the evaluation to the anterior wall. And so, as I indicated, the diagnostic performance was calculated by-segment, but I assume that to be identical to the by-patient analysis.

Here are the performance measures. Again, you can see the spread. A sensitivity of 75 percent, well, a sensitivity of 53 percent is equally consistent with the data, as is a sensitivity of 90 percent. So the small sample sizes -- or specificity, perhaps this is even better, of 67 percent, a specificity of 38 percent is equally consistent with the data. And so what to make with these specific numbers is hard to determine.

The strengths include, it was a consecutive study of prospective patients. All 39 patients were

included in the analysis. I've indicated that the by-segment analysis was equal to the by-patient analysis. Wall-motion assessments included evaluation of not only wall excursion, in other words, is it moving hypokinetic or dyskinetic, but also is it thickening. That is a somewhat more specific way of assessing true regain of function, because there is a tethering effect within the heart and segments can appear to move even without thickening even if they haven't regained their function. And so systolic wall thickening adds a certain level of specificity in this particular study to the assessments of wall-motion.

Major limitation, that the doses were not specified in the paper, the number of readers were not specified, and it didn't indicate whether the readers of the echo or PET were blinded. One other potential limitation of this is that performance measures such as sensitivity and specificity that are calculated for the anterior wall may not be the same for other regions of the ventricle, may not be the same for the lateral wall. And so that's a potential limitation of this study.

The next study is by Gropler. The objective was to determine whether prediction of recovery of left ventricular mechanical function could be accomplished more effectively by PET with carbon-11 acetate, which is a marker for oxidative metabolism, than FDG. This was a

comparative study. Again, it enrolled patients with coronary artery disease, left ventricular dysfunction.

Doses were assessed with a carbon-11 acetate, not the usual perfusion agent that jumps to mind when people think about it. The dose was not specified in the paper but was referred to in a reference. Quantitative image evaluation, 8 segments, but in this case viability in terms of a threshold was defined if FDG glucose normalized to flow was more than 2 standard deviations above the mean in controls. Revascularization was accomplished with CABG or angioplasty. And wall motion was assessed by each of the different methods -- echo, contrast, and radionuclide ventriculography -- on 5-point ordinal scales by blinded readers.

Thirty-four patients were evaluated. If you go back to 8 segments per patient, that comes out to 272 possible segments. Again, only the 141 that were dysfunctional at baseline were assessed. Of those, 116 were included in the analysis, and 46 of which had improved function.

And so these are the measures of diagnostic performance. And if this isn't immediately evident to folks, when I'm referring to prevalence here, what I am referring to is the 46 hibernating segments that regained function out of the 116 that were included in the analysis.

And that's true for all of these tables that I've shown.

Again, wall-motion analysis was performed by two, blinded readers. Well, it is an advantage to have more than one blinded reader or to somehow show that the results are not idiosyncratic to a particular blinded reader, or at least to be able to assess whether there is some sort of inter-reader variability. And so that's one common theme that I've emphasized, is whether the wall-motion analysis or the PET analysis was performed by one or multiple readers.

This study used several different modalities. It used echocardiography, contrast ventriculography, PET, radionuclide ventriculography. And somehow there has to be measures taken in a study that show that the segment under one modality is the same segment that you're looking at another modality. And this study was fairly detailed in terms of the way it laid that all out. I would like to emphasize that was one of the highlights or one of the strengths of this study.

This study also performed an ROC analysis, which in some ways you could view as being hypothesis-generating as opposed to hypothesis-confirming, because the goal is really to try to identify a threshold from the ROC curve that will give you optimal performance. But, on the other hand, an ROC analysis allows you to look at all the

data. Instead of assessing just one arbitrary threshold of FDG uptake at above 50 percent or below 50 percent, this analysis allows looking at every single data point and essentially allows for a true exploration of the data in terms of different thresholds. Moreover, it allows for a truer comparison of different diagnostic modalities. The purpose of this study, which I'm not emphasizing, was really to compare the performance with C-11 acetate with FDG. And ROC curves, oftentimes by showing all the data you can see whether the curves intersect or not, whether they cross one another, and so forth. And so that's a useful way of comparing two diagnostic modalities.

Some of the limitations. Again, not the prototypical perfusion agent was used. The number of readers wasn't specified. Ideally, there should be more than one. Blinding of the PET readers was not specified, although grace can be given for that because it was a quantitative analysis. And as is true for many of these studies, global and left ventricular function and clinical outcomes were not assessed. Again, many of the studies just stopped at seeing whether regional myocardial function had improved or not.

The next study was by Knuutie, et al. It was to assess the value of PET FDG in predicting cardiac wall motion recovery after revascularization. It involved

consecutive patients with previous MIs who had wall motion abnormalities at rest. Perfusion in this case was assessed with SPECT either with thallium or tecnesium-99. So, again, this underscores that different perfusion agents were used in these studies.

The dose of FDG was 7 plus or minus 1.5 millicuries, and segments were deemed to be viable if FDG uptake was above the lower limit of normal segments. Each left ventricle was broken up into 8 segments. Revascularization was accomplished by CABG or angioplasty. Wall motion, one blinded reader by echo on a 4-point ordinal scale.

There were 48 patients, times the 8 segments gives you 384 possible. There were 106 abnormal at baseline, 90 of whom were successfully revascularized, 27 of whom recovered function. So the prevalence of abnormal segments or hibernating segments in this particular study was 27 that recovered function out of the 90. And diagnostic performance was calculated by segment. Again, here is performance measures.

One thing this study did is it also determined an optimized threshold for sensitivity and specificity with a discriminate analysis, without consideration of perfusion. And these were the performance measures that were obtained, which are substantially different, as you

can see on the previous. Specificity was fairly low, whereas sensitivity was high.

This was the largest study I think. It had 48 patients. Wall-motion analysis was performed blindly. Again, alignment of different modalities. Even within PET, if it is done at different times, if the studies are done at different times, some statement should be made about how the segments were aligned. And, in fact, there was actually a formal statement in the paper about how reproducibility of wall-motion analysis was assessed by the same reader over time.

Some of the limitations. Again, some of the studies just indicated that the study was blinded, but it didn't say to what. That is potentially a problem because the wall-motion analysis, were they blinded to the PET studies, were they blinded to the clinical history, were they blinded to anatomic orientation; it is unclear. And so a further level of detail would be helpful.

The number of readers was not specified. The blinding of whether the PET images were blinded or not was not specified. And, again, there was no overall improvement of assessment of how did the patient do, or at least how did the whole left ventricle do.

The next study by Lucignani, et al. To identify hibernating myocardium with tecnesium SPECT

compared to PET. Again, same story, coronary artery disease, left ventricular dysfunction. Perfusion, again assessed with SPECT. 6.8 millicuries was done. Now here, this was one of the few studies that actually did a visual analysis of PET; most of them had some sort of quantitative assessment. And so this was fairly unique in that regard. The degree of uptake was assessed on a 3-point ordinal scale.

The success of revascularization was assessed by rigorous means, by coronary arteriography. And wall motion was assessed, in this case, with EKG-gated planar perfusion scintigraphy or first-pass radionuclide angiography, depending on the circumstance. But the number of readers was not specified, and the blinding of readers was not specified. This basically boiled down to whether or not the wall could be seen with the planar perfusion scintigraphy, and, if it couldn't, then the wall motion was assessed with first-pass radionuclide angiography.

There were 14 patients, a small study, 5 segments per patient, 54 of them were asynergic at baseline, 40 of which improved. And so the prevalence of hibernating myocardial segments in this study would have been 40 over 54, as we'll see on the next slide. And, in addition, two multiple logistic analyses were performed. And so the prevalence was 74 percent. Here again we can

see some of the spread that is a result of the small sample sizes. The specificity numbers of 52 percent and 96 percent are equally consistent with this dataset.

Two multiple logistic analyses were performed that showed the highest probability of wall motion recovery was associated with both F-18 FDG uptake as well as absent perfusion. So that is sort of the extreme what we call flow metabolism mismatch. A second multiple logistic analysis was performed without perfusion that showed even without perfusion the probability of wall motion recovery was increased as FDG uptake increased.

Strengths. I put down the qualitative evaluation as a strength because there may be circumstances in which, although it is debatable, there may be circumstances in which qualitative evaluations may be performed instead of quantitative ones. And it is useful to show that the results can be confirmed by the human eye and aren't just an artifact of some quantitative measurement of instrumentation.

They had multiple readers using evaluation of FDG PET and the perfusion images. And stress hypoperfusion was also evaluated. This is one of the few studies that evaluated stress hypoperfusion. Most only evaluated hypoperfusion at rest. So this is sort of looking at hypoperfusion sort of at yet another level and sort of

broadening the scale, which was interesting.

Again, major limitations. Small sample size. They didn't specify if the readers of PET and SPECT were blinded to the results of the wall motion analysis. The number of readers to the wall motion analysis was not specified, and it wasn't specified if the wall motion analysis was blinded.

I apologize if this is getting somewhat tedious. We have a few more studies and I'll try to go through them quickly.

A study by Maes to evaluate the ability of tecnesium MIBI to assess viability compared to PET with FDG and ammonia. 10 millicuries given. Viability was done by looking basically at flow metabolism ratio. Revascularization was through CABG only. Regional ejection fractions were calculated to assess improvements in regional ventricular function. So this is the one study, if I remember correctly, that did not use visual scales of hypokineses, dyskinese, askinese, et cetera. It actually used regional ventricular ejection fractions to assess whether the myocardial ventricular function was recovered or not.

Twenty-three patients. Relatively small sample size. This is the other study that only looked at the anterior wall. One other aspect of this study is that

biopsies were done at CABG. And so this is one of the few studies that actually had some sort of morphological correlates as well to estimates of viability. So if you would like to refer to that as a standard of truth on a morphological sense, I suppose you could. But again, this is a case where the by-segment analysis is going to be identical to the by-patient analysis because only one segment per patient is being evaluated, that is the anterior wall segment.

So, again, you can see the numbers. Wide spreads because of the small sample size. And as I indicated, morphological correlates were evaluated, which basically showed there was more fibrosis or greater degrees of fibrosis with greater likelihood of nonviability, as predicted.

Again, number of readers not specified. It wasn't specified if they were read blindly.

A study by Marwick, the goal of this was to assess the metabolic response of hibernating tissue as assessed by PET imaging again with a different perfusion agent, though, rubidium in combination with FDG. Revascularization by CABG or angioplasty. Two blinded readers, 6-point ordinal scale. Only 16 patients.

Here's the performance measures. Again, wide variation.

Strengths. Blinded evaluation of 2-D echoes, PET scans, and rubidium scans. More than one blinded readers. Stress hypoperfusion was assessed and post-exercise FDG uptake was assessed. So, again, this is looking at sort of a different end of the spectrum or pushing the spectrum of perfusion abnormalities a step further than most of the other studies did. Interestingly, in this study perfusion and PET studies were performed after revascularization as well.

Most of these points I've already covered. Although this study did look at symptomatic improvement in patients. It was one of the few that did. However, the conclusion was simply that the patients had improved angina compared to before revascularization. But from the perspective of understanding whether FDG somehow could have predicted that improvement, there was no specific analysis that was done. In other words, that improvement in angina could have just been from the revascularization alone and may not at all be correlated with the degree of viability as predicted by FDG at baseline.

Tamaki, there are two studies by him and his colleagues. I don't see anything particularly unique here, except that this is one of the few studies that actually looked at patients with fasting. Most of the other studies were done on top of glucose load. There are advantages and

disadvantages to doing that, but this is one of the few studies that did it.

Revascularization was by CABG alone. The quality of the revascularization was assessed by evaluation of improvements in perfusion with ammonia. So a fairly rigorous criterion. And wall motion analysis was assessed by radionuclide ventriculography by three blinded readers. Only 22 patients, 110 possible segments, only 46 of which were included in the analysis, 23 of which regained function. Here are the performance measures.

Strengths. Again, multiple blinded readers, rigorous assessment of revascularization, good discussion of alignment of segments before and after revascularization as obtained by different modalities, as well as by PET before and after revascularization.

Limitations. Small sample size, and very, very little information about the study subjects was provided in this paper. And that is an important point because in terms of knowing to whom this study is generalizable, it would be nice to know the ratio of men and women, basic demographic aspects of the patients, the nature of the coronary artery disease, how severe the left ventricular dysfunction is, and all those other sorts of details to know whether this particular study is generalizable to larger populations.

Another study by Tamaki and his co-workers. Again, done under fasting conditions. Again, viability assessed by a match/mismatch pattern. Three blinded readers for the wall motion on a 5-point ordinal scale. Forty-three patients, one of the larger studies in that regard. So that would be 215 possible segments, of which 130 were included. And here is the performance measures.

Again, of the ten studies, this was the second largest. Wall motion analyses were performed by multiple readers that were blinded. Rigorous assessment of the success of coronary revascularization. This is another case in which all it said was that the readers were blinded but it didn't say to what they were blinded, again, an important thing to include in the manuscript.

And this final study is actually one of the original seminal papers in the field, it is by Tillisch and co-workers, published in the New England Journal of Medicine in 1986. There were many, many aspects of this study that were well done. It is a fairly small study. I point to it because there is not particularly anything unique that I can emphasize now that I've been through the prior nine studies, but just that there were many aspects of this study that were well done even though it was a small sample size. These were the performance characteristics that were measured.

So strengths. Wall motion assessed by multiple blinded readers, consecutive patients were enrolled, these were all prospective studies, success of revascularization was assessed, and the alignment of myocardial segments was described across modalities.

Small sample size. Didn't specific the number of readers of PET, didn't specify whether the PET readers were blinded. Again, this is another case where very few patient characteristics were described, so it is hard to know what the patient population was to whom those results may be generalizable.

Now I'm going to go fairly quickly through the secondary published literature. I provided a summary of it in my review. What I was looking for in the secondary published literature was really a few things, which are highlighted on the next few slides.

I wanted to see whether there was any literature that supported the clinical usefulness of PET with F-18 FDG. In other words, it is not enough just to show that the segment improved but that the heart didn't or that the patient didn't, but rather what is the evidence that it is clinically useful or that it leads to appropriate clinical decisionmaking, and to provide support that cardiac PET imaging, as I just said, influences clinical decisionmaking appropriately. It is not enough

just to influence clinical decisionmaking, but it has to be influenced appropriately.

I also looked at the secondary published literature to see whether regional left ventricular function was associated with global left ventricular functional recovery. And again, as I emphasized at the beginning, to see whether those pharmacodynamic endpoints are translated into clinical meaningful endpoints, such as improvement in symptoms, improvement in exercise tolerance, or prolongation of survival.

Now when we get into this sort of level, we're talking about levels of claims that are slightly further down on the scale in terms of being able to appropriately influence decisionmaking or whether influencing clinical outcomes and diagnostic and therapeutic management. And so the argument that I am trying to make here is, basically, I didn't feel that the evidence was sufficient from these papers to uphold that sort of a claim on that level. However, it was sufficient in the aggregate when you looked at those studies to support a claim of detecting myocardial hibernating tissue.

Safety, basically no additional safety concerns were raised by some additional information that we've received at the agency as well as in the original NDA. I mentioned the issue of glucose load or fasting, which isn't

an issue of FDG, per se, but it is an issue of perhaps how the drug is used.

And so my preliminary conclusions, and this is analogous to slide number 3 except that it contains the descriptor of who the patients are, is that the literature supports the use of FDG in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging, to identify left ventricular myocardium with altered glucose metabolism and reversible loss of contractility. That's a long sentence.

One thing I would like to emphasize is that all these studies, for the most part, they only looked at the case of successful coronary revascularization. Most of the analyses were limited to that case and so that may actually limit the usefulness of PET imaging.

In other words, on the one hand, being able to evaluate the performance of FDG in only those patients in whom revascularization was successfully completed eliminates the variable revascularization from the analysis and gives you a truer assessment of the performance of the drug without other competing, confounding influence. However, if the patient is unlikely to have a successful revascularization, then that would influence whether or not a PET imaging scan with FDG would be obtained or not,

because if it is unlikely to be successful, then regardless of how good the test is, viability would likely not recover spontaneously. And so the likelihood of successful revascularization should be considered carefully by health care providers before imaging with FDG is performed.

And in terms of safety for the use for cardiac evaluation, it generally appears to be safe. However, patients with impaired glucose homeostasis may require special precautions if they undergo fasting and/or glucose loading prior to drug administration.

Thank you.

DR. RAMSEY: Thank you very much, Dr. Raczkowski.

I think we will actually hold questions for now. I have had a request by Dr. R. Ed Coleman, from Duke University, to go ahead with his presentation at this time, and so I would like to ask him to come to the podium. We will hold questions until after his presentation, and then we will have open public forum and time for questions.

Also, I would like to alert the speakers for this afternoon that although the questions have been excellent and lively, I have no idea exactly how many there will be and it may very well be that your presentations will be slightly before the time stated. So if you could just be prepared for that.

DR. MADOO: Dr. Coleman, if you would, identify if you were conveyed or sponsored by anyone.

DR. COLEMAN: My name is Ed Coleman, I'm from Duke University, and I am sponsored by the Institute for Clinical PET.

I would like to compliment Dr. Sancho, Dr. Laniyonu, Dr. Houn, and Dr. Raczkowski for the presentations they have given us here today. What I'm going to do is to focus on the uses of FDG, and particularly my experience with the use of FDG primarily in oncology. I'll make a couple of statements about its use in cardiology. Dr. Maddahi will be talking later on in the open session after the N-13 ammonia presentation. And as you've heard, the FDG is generally used with a perfusion agent and in most institutions with N-13 ammonia. And Dr. Maddahi will talk a little more about its clinical applications.

Let me start off with a patient that was studied recently at Duke University. This was a lady that presented to the gynecology service, had a routine chest x-ray, and has a right upper-lobe nodule. And by chest x-ray, this is indeterminant; by looking at that, cannot determine whether that is benign or malignant.

The next study that was done was a CT scan. And, again, on the CT scan we see this abnormality in the

right upper-lobe, no characteristic findings that suggest that it is benign or malignant. And so, again, this is an indeterminant pulmonary nodule. This is a single pulmonary nodule. On the CT scan there were no other abnormalities that suggested malignancy. The lymph nodes in the mediastinum were normal, the bones that were seen on the chest CT were normal. So we were left with an indeterminant lesion in the right upper-lobe.

The next procedure that was obtained in this patient was a radionuclide bone scan. I think one could question why that was obtained at this time, but it was. At this time, again, we had no diagnosed malignancy. The clinicians were very concerned that this was going to be lung cancer. The bone scan is, as you see it here, in the left iliac wing we have a focal area of abnormal accumulation. I would like for you to look at the spine, look at the sternum. No other abnormalities.

So at the time of the bone scan we obtained a plain film of the pelvis to see if there was a diagnostic lesion that would suggest malignancy. There was not. The plain film was normal at the site of abnormality on the bone scan. In a patient with a malignancy, that is very worrisome for metastatic disease; that is, an abnormal bone scan, normal plain film. The bone scan is more sensitive for detecting metastatic disease than is the plain film.

But with this patient not having a malignancy, no abnormality, a little bit of a quandary as to what this would mean.

The clinicians then ordered a whole-body FDG PET scan, which I'm showing two of the coronal sections here, two of the more anterial coronal sections. And what we are seeing here is abnormalities, this is in the sternum, and mediastinal lymph nodes on these two sections. We do see that left iliac wing abnormality on that coronal section. And as we go a little further postoral, we're seeing the right upper-lobe nodule, demonstrating that it is malignant, other mediastinal lymph node abnormalities, and multiple vertebral body abnormalities. In addition to the left iliac wing abnormality, there was a right iliac wing abnormality.

So we're seeing multiple lesions here that had not been detected on the other studies. More detailed views of the chest show this right upper-lobe nodule, mediastinal lymph nodes that were all less than one centimeter on the CT scan, multiple vertebral body abnormalities, and if we look at this what we call a sagittal, or more side, view, it gives you more detail as to where the abnormalities are, in the sternum multiple vertebral bodies and in the mediastinum. So this is the type of information that we are able to obtain from the PET

scan.

We have heard today that we're looking at fluorodeoxyglucose. It is a biochemical marker. The use of this really dates back to the findings of the biochemist Warburg, who in 1931 reported that tumor cells metabolize glucose avidly. Then Dr. Sokoloff at the NIH worked on the 2-deoxy D-glucose to show that you could look at glucose and quantify glucose metabolism using the deoxyglucose technique. The radiochemist Al Wolf and colleagues at Brookhaven National Laboratories then synthesized the fluorine-18 to fluoro 2-deoxyglucose that we now use for the PET scanning.

You have heard this gone through a couple of times today, that the similarity of the behavior between the fluorodeoxyglucose and glucose is the basis upon which this imaging principle works. Just a couple of points that have been brought out here, is that the PET scans are done with the patient in the fasting condition. We want the blood glucose level to be at the lowest level it can be but we don't want the insulin levels to be sky-high either. That is, if you inject insulin at the same time you inject FDG, most of that FDG is going to go intramuscularly. And so it is a balance between the serum glucose, serum insulin, and the fluorodeoxyglucose.

So, typically, we have our patients fasting

four hours before having the study. If they are scheduled first thing in the morning, they are fasting over night. If they are scheduled later in the day, it is a four-hour fast. If the patient is diabetic, we want them to be at as uglycemic normal glucose levels as they can be. And, typically, what we have used as a cut-off in our laboratory is a blood glucose of 200. And for patients who are diabetics, we ask them to have their glucose under control without having any regular insulin within four hours of coming to the PET laboratory. Patients these days are very knowledgeable about their glucose levels and they can get their own glucose levels to the point where it will be at an acceptable level when they come to the PET facility.

If for some reason a patient is diabetic and did not know that they were supposed to be fasted or what their glucose level was going to be, we will check the glucose level in the laboratory. But we do not do it routinely. It is only if they are diabetic, if there's any question of not fasting for four hours, or any question of glucose intolerance, then we will get a serum glucose. And we do not do the FDG study if the serum glucose is greater than 200.

This shows what has been happening to PET imaging at our center, Department of Radiology, Duke University Medical Center, going back to December 1996.

The yellow are the total studies, the orange-ish line here is the clinical studies. And you can see back in 1996 we were doing 40 to 60 a month. Now we're up to 180 a month, and this year we will be doing about 2,000 clinical PET scans. So this is a timely topic. It is a very important topic for us in nuclear medicine, in radiology and PET imaging to make sure that we do have these radiopharmaceuticals approved and that they are being used under the right regulatory authority.

What I'm going to do now is go through the patients that we did last Wednesday. We do eight to ten clinical patients a day. I thought it may be useful for this panel just to see what types of patients does a PET center see in a day of activity.

This first patient is a patient with a history of a brain tumor. He has had resection, and the question now is does the patient have a recurrent tumor or not. The data on supporting this indication was the first clinical PET data in the literature. And really, clinical PET was started by Giovanni Di Qierro and his colleagues at the NIH. Giovanni did some very careful and important work on looking at FDG accumulation in brain tumors and in differentiating necrosis from recurrent tumor after therapy. During the discussion, there was some discussion related to the metabolic information and the prognostic

information in the imaging studies. Well, Giovanni Di Qierro many years ago demonstrated very clearly that the more metabolically active the tumor, the shorter the prognosis, and regardless of what the histologic characterization was, the metabolic information provided better prognostic information than did any other parameter.

We have shown in lung cancers, and this was published in Cancer this year, that lung tumors that are more metabolically active, have higher SUVs, have a much worse prognosis than those that have low SUVs. And there is similar data, again from the NIH and other institutions, on soft tissue carcinomas. The higher the amount of FDG uptake, the more malignant carcinoma it is. So there is data out there in certain tumor types on using FDG from a prognostic standpoint.

What I am showing on this slide is a patient who has had surgery. The question, recurrent tumor. On the left is the patient's MRI, contrast enhanced MRI, and on the right is the registered PET image. That is, we've take the PET and MRI and matched the surfaces so that we can move from one to the other and look at the exact same structure. And this image is two-thirds MRI, one-third PET. This is two-thirds PET, one-third MRI, and then 100 percent PET. What we're seeing is there is some glucose metabolism, not great, but in this little nodule of

enhancement here just posterior to the cystic cavity. The other are radiation changes, enhancement from necrosis, but there is recurrent tumor in this patient. And this is the combination of the findings from the MRI and PET that permit us to make that diagnosis.

This is an interesting patient that I don't have pathology back on as yet; I checked yesterday before I left to come here. She has had two lymph node biopsies and neither one has been diagnostic. She was referred to Duke earlier this week with some shoddy adenopathy in the neck, she had a right axillary node, and on chest x-ray has a mediastinal mass. Certainly highly suspicious for lymphoma.

Before she got to the PET facility, they had biopsied a right axillary node that came back non-diagnostic, maybe slightly increased plasma cells but no characteristic lymphoma. We did the PET scan, and you can just see nodes, 50 to 100 of them in the neck, mediastinum full of nodes, superclavicular fascia, both axilla, mediastinum into the hyla areas, spleen is involved, periaortic, abdominal lymph nodes, iliac, and inguinal lymph nodes. So, certainly, this should be lymphoma. I notice on Friday they biopsied one of the abdominal nodes under ultrasound guidance, and, again, that had come back nondiagnostic. But this very likely will be lymphoma, and

very likely a Hodgkin's lymphoma.

This next scan is a 52-year-old gentleman, actually an administrator at the hospital, that has been a very active runner, very avid athlete for many years. Over the last couple of months, he has had the insidious onset of back pain. He was treated conservatively for six weeks or so. Back pain continued to get worse. Started having some fever, just general not feeling well. And was admitted to the hospital last Sunday night mainly for pain control. On Monday, he had an MRI that shows diffuse increased T-2 signal in T-11. Worrisome for myeloma, worrisome for lymphoma, unlikely to be trauma, doesn't look like a fracture. He actually got his CT scan. The CT scan was negative. I should say there was slight contrast enhancement on the MRI. He got a CT scan that was negative. Had a biopsy of that vertebral body. It came back normal bone and bone marrow.

Got the FDG PET scan. It shows increased signal, increased FDG localization in the T-11 vertebral body, on coronal sections, we're seeing the increased FDG accumulation there. The patient went to open biopsy on Friday, and those results are not back as yet.

This is a patient that recently presented. On a chest x-ray had two nodules, one in the left upper lobe, one in the right upper lobe. The left upper lobe nodule

was biopsied. A small cell lung cancer. We also see hypermetabolism in the right upper lobe nodule, suggesting another lesion. Here it is on the transaxial sections. The right upper lobe nodule. The left upper lobe nodule was actually right up next to the aorta.

What the PET scan was able to show here were two lesions in the liver; a small lesion here in the right lobe, and a larger lesion in the left lobe. The left lobe lesion on CT scan was seen and thought to be possibly a cystic lesion and not definitely a metastatic lesion. The right lobe was not see on the CT scan.

This is a patient that presented to the thoracic surgeon with a barium swallow showing an esophageal mass. This is presumed to be esophageal cancer. What we're seeing on this coronal section is increased uptake in the distal esophagus. We're seeing it here. On a more localized view of that area, we're seeing the FDG accumulation in the esophageal cancer. We're seeing a lymph node right below the gastro-esophageal junction that had not been caught on the CT scan. In retrospect, you could go back and see that lymph node. But the tumor is also extending into the superior portion of the stomach, and, again, suggested on the barium swallow but had not been called at the time of the barium swallow.

This is a patient with rectal cancer with a

known three centimeter lesion in the liver. The patient is being considered for operative resection of the metastatic disease in the liver. It has been found that a third to maybe as high as 50 percent of patients that have colorectal cancer metastatic to the liver may significantly benefit and have prolonged survival with removal of these lesions if the tumor is not elsewhere.

And so this patient had a CT scan showing the one large lesion. There was an equivocal abnormality lateral to that, which we're seeing here on the PET scan. There are two lesions here. And again on these images you can see the larger lesion and then the smaller lesion is seen a little better postoral. There are several studies in the literature now that show the accuracy of PET scanning in detecting metastatic cholorectal disease and the advantages of its use for the surgeon in defining the disease.

This is a patient that had had colorectal cancer metastatic to the liver that had had a hepatic resection of the metastases, and this was being for follow-up is there recurrent tumor on these whole-body coronal sections. This is a normal study. As we look a little more postoral, we can see the evidence of the resection. We're seeing evidence of resection here. But there was no evidence of recurrent or persistent tumor at this time.

This is a PET scan of a 19-year-old boy with malignant melanoma that had recurred in his axillary lymph nodes right axilla. He had had surgical removal of those. Now this was being used to determine is there any persistent or recurrent disease. And we see no abnormalities to suggest recurrent melanoma on this patient.

The next patient is an older patient than the last. This patient is in his 50s. Very similar story. Had a melanoma removed several years ago, then developed axillary involvement, had surgery, now coming back six months later is there any evidence for metastatic disease. And in this patient we have right upper lobe metastases, left iliac wing metastases, and a left adrenal metastasis. So this is being used to for surveillance of these patients to determine when the disease has recurred.

And then, just in closing, to show FDG in determination of cardiac viability. Dr. Raczkowski and others have pointed out that we compare the FDG images, which are these three images, with the ammonia images, which are these three. On the vertical long axis views on this ammonia image, this should look like a horseshoe. And so this portion of the myocardium is hypoperfused. If you look at it on the glucose, it has FDG accumulation within it. So that shows that it is ischemic, decreased blood

flow, but viable, having glucose accumulation within it.

This particular patient is a 60-year-old woman, 8 years post-bypass grafting surgery, 6 months post-anterior wall infarction, heart failure EF-22. The images revealed this mismatch consistent with viable anterior wall. Coronary angiography revealed an occluded graft. A second bypass was performed. Six months later the patient was asymptomatic. Ejection fraction 47 percent.

And then the last one is a 30-year-old man. Family history of heart disease. Anterior wall infarct. Angioplasty attempted. Unsuccessful. The PET FDG and ammonia images show a match consistent with scar. Because of the age, 32, they chose to go ahead and bypass the patient. Two months after cardiac surgery, the pre-surgical ejection fraction of 20 percent was unchanged, wall motion not improved. The patient died six months after the surgery.

This shows the images in this patient. Again, this should look like a horseshoe. A large defect here in the anterior anoapical-infloapical wall. But the FDG images look identical to the perfusion images. So this is a match and shows infarcted myocardium, not ischemic myocardium.

Thank you.

DR. RAMSEY: Thank you, Dr. Coleman.

We have time for questions now for the speakers from this morning as well as Dr. Coleman.

DR. KONSTAM: Dr. Coleman, could I just ask you about that cardiac case with the viability. I think I noticed that there didn't seem to be an increase in FDG uptake in the ischemic, it just looked homogeneous relative to the flow which was clearly not. I guess the question I have is, to what extent is the diagnostic capability of FDG for viability a function of increased uptake versus just simply a mismatch with flow or wall motion?

DR. COLEMAN: The FDG images have been evaluated in several ways. As Dr. Raczkowski pointed out, there have been criteria based upon if it is greater 50 percent of otherwise normal myocardium, there have been pooled data to use as a background upon which to compare the FDG accumulation, and there has been visual interpretation. And I think most of us in our clinical practice look at the images and say is there more FDG accumulation there than perfusion, suggesting that there is ischemic viable myocardium. So it is a comparison with the amount of FDG in a region as compared to the perfusion to that region.

DR. KONSTAM: So the diagnosis doesn't really require an excess FDG uptake relative to normal?

DR. COLEMAN: No, it does not. Any FDG uptake

there suggests some degree of viability. And then you have got to compare it to the amount of muscle there that has perfusion. So, the answer is, yes.

DR. MALCOLM: I had a question for Dr. Coleman. Just a very simple question. I just wanted to know how do you report those positive studies in the oncological patients? If I was a clinician looking at any of those studies, what would the readings say?

DR. COLEMAN: The readings would say, for example, in a patient with a solitary pulmonary nodule, if I have FDG that looks like the one I showed you, these are the findings suggesting cancer. In the multiple abnormalities, these findings would be most consistent with metastatic disease. In the patient that I presented with the lymphoma, that distribution would be most consistent with lymphomatous disease. So that's the way my interpretations would be.

DR. TATUM: I'm Dr. Tatum. Another question for Dr. Coleman, because I think it is really important for this panel to understand, and a question that has come up several times, in comparing why there is not a sponsor. If this were another type of a drug with a broad dissemination and profit margin that was more extensive, we would expect to see a sponsor. So that becomes a very critical point. And I would like to hear, I know you've been in the area

for a long time, your comments on why you think there isn't sponsorship, and what impact it has on our decisionmaking process.

DR. COLEMAN: Well, I think that to go through the NDA process, to go through the clinical trials is a very expensive process. There is no company out there that is going to make the amount of money that is generally made on drugs that receive an NDA, so there is no impetus for any one company to support the clinical trials that are used to have an NDA for a drug like this. The ICP in its very inception met with the FDA to go through this type of process for approval for FDG just because of that reason. And so I think this is a very reasonable process to go through for the PET radiopharmaceutical drugs where there is no proprietary nature to the drug.

DR. AMENDOLA: I'd like to ask a question to Dr. Coleman regarding his experience on the use of this agent in breast cancer. There is a very specific set, a patient with a negative mammogram, a positive MRI, the patient cannot be biopsied. It seems that that would be a pretty good indication for this.

DR. COLEMAN: The data on using PET imaging for characterizing breast lesions is relatively sparse at this time. The initial data are somewhat promising. I think that for breast imaging what we are going to find is the

development of specific devices that will improve the resolution for detecting breast lesions, so-called positron emission mammography. And several centers now are working on such devices to be able to improve the resolution for detecting breast lesions. So the preliminary data look quite good for breast cancer, look quite good for looking in the axilla. But I think that it is going to get better when we have the dedicated devices.

DR. RAMSEY: Dr. Coleman, you will be here this afternoon if there are any more questions?

DR. COLEMAN: I will.

DR. RAMSEY: Okay. Does anybody have any more questions?

Yes?

DR. HAMMES: Dr. Coleman, your experience with FDG, in particular, but also the ammonia and water, have ever witnessed any adverse effects?

DR. COLEMAN: I have never witnessed an adverse effect. I called Dr. Ted Silverstein, who chairs the Pharmacopeia Committee of the Society of Nuclear Medicine, who surveys all PET centers, and I think it is on a monthly basis, I think we send in monthly reports, but he surveys and he has never received a single adverse event from a PET radiopharmaceutical.

DR. HAMMES: Also, does the FDA have any

reports of adverse effects from any of these agents we're talking about?

DR. COLEMAN: In his letter to me, he said they did not. But I don't know.

DR. LOVE: Since water or ammonia at this moment are not under NDA, we would not normally receive reports from them, it would only be from FDG. And to my knowledge, we have not received any report on FDG.

DR. CHOYKE: Dr. Coleman, could you say what the relative percentage of oncologic versus cardiac use is in your place, and then overall.

DR. COLEMAN: The overwhelming use of FDG clinically is in oncology. Of the 2,000 clinical PET scans we do at Duke, this year the number that will be cardiac will be somewhere between 50 and 100 out of those 2,000. And I think that that's not too dissimilar from most active PET centers. There is going to be a few, like UCLA, that has done a lot with cardiac PET and will have a little different ratio and use it more for cardiac. But most of my colleagues that have active PET centers where there is a lot of oncology and cardiology, it is heavily weighted in favor of oncology.

DR. RAMSEY: Any other questions?

DR. KONSTAM: Just to follow up on that, and it gets into a question of physiology that I have. I wonder

why it isn't used more in cardiac, in your experience anyway. I guess I want to couple that with sort of a quandary that I have about the dataset in general; which is, there's a significant nuclear medicine literature on myocardial perfusion imaging as an indicator, and maybe I can address this to Dr. Raczkowski as well, as an indicator of viability, that is perfusion as an indicator of viability. And there is extensive literature about this. And yet when you turn to the PET literature, you're looking for a mismatch that is under perfusion relative to FDG.

I guess let me perhaps partly answer the question relative to what we said earlier, is that, well, but maybe there is increased uptake of FDG in the ischemic area, so it is going to be still increased relative to perfusion even if perfusion is relatively normal at rest. But then, on the other hand, you showed us a case that didn't have increased FDG perfusion. So, I guess I'm not sure it matters in the end of the day in terms of the data that Dr. Raczkowski showed which seemed to show that it is useful. But I just wonder if either of you, or anyone else, can comment about this I think little bit of a paradox.

DR. COLEMAN: Let me say a few things, and then maybe Dr. Maddahi will want to say something, too.

Why is this not used more? I think that there

is a lot of competing techniques out there that are pretty darned good right now. Thallium redistribution is pretty good. Low dose dobutamine echo is pretty good. FDG PET is probably a little better than those but it is not as widely available. Cardiologists are more used to using the low dose dobutamine echo or thallium. And so it just hasn't been used that much.

Now concerning the use of perfusion alone in predicting viability, certainly if you get below a certain threshold of perfusion, you are not going to have viable myocardium. And this has been shown in dog studies as well as in people. But above a certain level, it is difficult to know whether that is going to be ischemic or infarcted. And I think that that's the group where the wall motion stops, the wall stops functioning, the perfusion is decreased, it is not zero, there is some chance for viable myocardium but it also may just be ischemic and viable. And so that's where the PET technique helps.

Dr. Maddahi, did you want to say something there?

DR. MADOO: Can you identify yourself and your affiliation, whether you are being sponsored.

DR. MADDAHI: Yes, my name is Jamshid Maddahi from UCLA, and I am sponsored, like Dr. Coleman, by ICP to appear here.

I agree with the comments that Dr. Coleman made about the two issues. But I would like to add a little bit to it. Why isn't it used as much? I think that part of it is because of the fact that there are other techniques that do the job. But also we have got to keep in mind that even in centers that do cardiac studies, 20 cardiac studies a day with nuclear techniques, the ones that directly and specifically relate to myocardial viability are not many studies.

Even in those centers, only about two a day are related specifically to myocardial viability because we're looking at a disease that the prevalence of the patient population that would require a specific question of myocardial viability is much less than it is for detecting coronary artery disease. So later on when we'll be talking about detecting disease with just ammonia, those are the type of studies that, if they are used, they will be used in the ratios, in the higher ratios than viability assessment.

The second question was related to perfusion and relationship to viability. We published a few months ago an article that we looked at actually the specific question of relationship of perfusion to myocardial viability. What we found was that below a certain amount of perfusion, generally there is not much viable tissue

because there has to be at least a minimum amount of perfusion to keep the tissue viable. And also, when you get to very high perfusion levels which is close to normal, 80 percent or more, or 20 percent only reduction in perfusion, then you'll see that those areas are also often viable and there's no problem there.

The clinical problems in perfusion levels are in the intermediate zone of somewhere between 20-25 percent to 70-80 percent. In those intermediate zones, then perfusion alone cannot distinguish the three different patterns of viability which we call hibernation, or stunning, or presence of the myocardial infarction, transmitter or nontransmitter infarction.

So I think that in clinical decisionmaking, when I see the perfusion defect that is very, very severe, very much reduced, I don't really need anything more to tell me that it is nonviable. And when perfusion is normal, I don't need anything else to tell me it is viable. But when it is in the intermediate zone, that is where the clinical problem starts and we need a metabolic marker to tell us whether it is viable or not.

DR. RAMSEY: Let's have one more brief question or comment, and then we'll break for lunch. We can continue the discussion after lunch.

DR. RACZKOWSKI: Victor Raczkowski. The only

thing I wanted to add to that is some of the agents that we're referring to as perfusion agents, such as thallium, have other properties besides just assessment of perfusion. Thallium requires an intact membrane in order for it to be taken up. So, in that sense, it could be viewed as a potential marker for viability as well, not just perfusion.

DR. RAMSEY: Thank you.

Again, I want to thank all the speakers and presenters this morning. I think we all learned a lot. Everybody did a very nice job.

Let's take one hour for lunch. We'll reconvene here at 1:30. We can continue our open discussion, and then we'll go right into the presentations. So have a nice lunch and I'll see you at 1:30.

(Whereupon, at 12:30 p.m., the meeting was recessed for lunch, to reconvene at 1:30 p.m.)

AFTERNOON SESSION (1:35 p.m.)

DR. RAMSEY: I sent Mr. Madoo out there to ring the bells. So we will see if we can get everybody back in here. All our good question people are out enjoying themselves. We have to get them back in here. Mr. Madoo is out rounding up the last members. But I think it is time, it's a few minutes past time, so why don't we go ahead and get started.

First, I would like to ask if there are any questions of any of the speakers this morning, or further conversation or comments regarding their presentations?

Dr. Hertzberg?

DR. HERTZBERG: What I'm struggling with right now is that for FDG for malignancies there is no restrictions with regard to safety, but for cardiology uses you've indicated a safety hedge, if you would, for individuals with impaired glucose metabolism. And I was just wondering if you can help me straighten out it should be in one and not the other, or why they should differ in that respect.

DR. RACZKOWSKI: I'm not sure that they should be different. One of the speakers, Dr. Coleman I believe, this morning indicated that in his experience generally patients are uglycemic or near uglycemic when they are considered to be candidates for PET scanning. Our

anticipation would be that the labeling would be similar for both indications.

DR. HOUN: I don't think that there was enough data to actually comment on its use in diabetic patients. So I'm not sure, if you saying there was no restriction in oncology, it is no data was presented on how hyperglycemic patients would react with a PET scan, what the efficacy would be with hyperglycemic patients. And in four studies, they specifically excluded patients with glucose over 100. So some of that would be reflected in the labeling.

DR. RACZKOWSKI: Right. And, actually, I raised it more also as a theoretical concern. It wasn't anything that I had seen adverse event reports that was resulting from data.

DR. LINKS: Jon Links. Just to also clarify. In the case of FDG, you have to make the distinction in these conversations between issues arising from the preparation of the patient versus an actual pharmacologic effect of the tracer itself. And in this context, there is no pharmacologic effect of the tracer itself.

DR. PONTO: Laura Ponto, the University of Iowa. I guess I would like to address this question to Dr. Love, Dr. Houn. How extensive do you anticipate the labeling to be with respect to patient preparation? Those of us who work with FDG know the importance of monitoring

the glucose, of having different types of glucose state, whether it is a fasting state for a neurological study or oncologic study, the fed state for a cardiac study. How extensive do you anticipate the labeling will be, and how much do you anticipate you would need to advocate that the glucose levels be monitored?

DR. HOUN: I think in looking at the studies that were reviewed, we would have enough to put in the label that the studies were done in uglycemic conditions. We don't have enough information about how it would be performed in a diabetic population, what the results would be. I think we would recommend in terms of dosing administration at least four hours or more fasting prior to the IV injection for the oncology indication.

What were the other kinds of concerns in terms of patient preparation? Should glucose be monitored?

DR. PONTO: Yes. Would you have them monitor the glucose? And would you put a precaution on for diabetic patients?

DR. HOUN: I would welcome your advice on that. I think we certainly would state that there was a lack of data to say what efficacy could be found in diabetic patients. One study specifically said four of their patients were diabetics. But the results from the other studies we don't really have. So whether that's a

precaution or a statement in the clinical trials section, it certainly I think deserves consideration. In terms of precautions, what we would be cautioning about was that there wasn't information to state about its effectiveness in this population.

DR. TULCHINSKY: If I may add to this just for a moment. Currently, as we're doing myocardial perfusion imaging with thallium, there is also very specific preparation procedure. Patients should be fasting, for a number of reasons into which we're not going to go at the moment. But would it be reasonable to leave that as a practice of medicine for an individual center to decide? It has not been really a safety problem. As a nuclear medicine physician, that would seem reasonable to me.

DR. MALCOLM: I was going to say this issue of safety and preparation is a medical problem and the referring physicians and the physicians doing the study should have information with regards to the patient's metabolic state. This has nothing, as I see it, to do with the drug itself. The drug has no "effect" on a patient that's diabetic. It is the fact that the patient may be a diabetic and can that patient fast, et cetera, et cetera. So that has to be a clinical decision that should be made prior to the patient having the study that the physician should be aware of. Aren't we all saying the same thing?

So it's kind of a different issue.

DR. TULCHINSKY: Exactly.

DR. KONSTAM: No, but the efficacy question, she's saying, if I'm catching it, that in your review of the literature you would raise a question as to whether the data are as clear in a diabetic population. Is that --

DR. HOUN: Yes, exactly.

DR. KONSTAM: So that that ought to be stated.

DR. HOUN: I don't know, the effectiveness in the diabetic population who are suspected of having tumors, that was not very well demonstrated and documented.

DR. TULCHINSKY: Yes, and that's very well understood. I am not contradicting in that respect. All I am saying is it hasn't been demonstrated to be effective, or it hasn't been demonstrated not to be effective. I would leave it to an individual pair of physicians on both the management team and diagnostic team to sort it out.

DR. KONSTAM: Maybe this does need a little bit more discussion because I'm worried that we're on a slippery slope. You know, we're here to determine the efficacy of the agent for the indication shown. And the presumption is that the agent is effective in the population in which it is going to be studied. And this needs to be data-driven. And to the extent that we're sort of falling back on criteria for data, there may be reasons

for that, but if, in fact, there might be some reason to suspect there might be less efficacy in diabetics and we don't have a dataset to deny that, then I think that that's a population that has not been studied and that needs to be reflected in the packet insert.

DR. TULCHINSKY: In what sense? Like what would you suggest? How?

DR. KONSTAM: Like what I just said. That the efficacy has not been demonstrated. And I don't know the data well enough, but what I gather just in listening to the presentation and reading it, is you're saying the efficacy has not been established in a diabetic population.

DR. TULCHINSKY: That sounds fine. It's a little bit troublesome though, because there are so many other conditions I guess that it hasn't been demonstrated. Should we list those too?

DR. RAMSEY: Mr. Hammes?

DR. HAMMES: At least in terms of cardiology, I had a discussion with a cardiologist before I came to this meeting and they expressed a very strong concern in terms of any kind of limitation on FDG for that population just because that's the population that has a great deal of cardiovascular disease. And along with that, they passed along to me an article, which I did bring along, from the April 1999 Journal of the American College of Cardiology,

that specifically looked at the use of FDG to assess left ventricular contractile dysfunction in a diabetic population with very good results. I think that is something we need to consider in these deliberations. There now is data out there.

DR. RAMSEY: Any other comments, questions?

DR. KONSTAM: I wanted to go back to Dr. Raczkowski's presentation. To begin with, I would like to critique the indication or the draft indication in a couple of respects. One is that I would urge taking the word "contractility" out of the indication. None of the studies measured contractility. Contractility is a specific indicator of myocardial function independent of load. And so what was measured was systolic function. And so that's really the way it ought to be stated.

The other thing about the indication, and I guess I was sort of asking about this before, you're talking about altered glucose metabolism. I'm not clear that altered glucose metabolism is the key element, or, if it plays a role, whether it is a necessary element in the diagnosis here. At least to a great extent, the diagnosis is based on a mismatch between glucose uptake or FDG uptake and either perfusion or wall motion. So I think that is really the key element. I don't believe that we've shown that a key part of the diagnostic role is in identifying an

abnormality of glucose metabolism; it may or may not be.

So I redrafted it and it can just be played around with. I said, "To examine myocardial glucose metabolism and to identify myocardium with reversible loss of systolic function, when used together with myocardial perfusion imaging." Something like that to solve those problems.

DR. RACZKOWSKI: I absolutely agree with you about the contractility statement and systolic function. One of the reasons we put the glucose statement into the indication was just to have some statement in there reflecting the underlying biochemical.

DR. KONSTAM: Oh, yes. But I'm just saying it is not necessarily an abnormality of glucose metabolism. I would just restate it a little bit so that it's not -- that's why I said to examine myocardial glucose uptake or metabolism, however you want to say it.

The other question I had, I just wonder whether, in looking at the data, again with regard to the myocardial indication, whether it might not be subject to a meta analysis. Understanding that there are a lot of differences in there, but I think still there's a lot more similarity across those studies relative to comparatively to the cancer indication. I think that might be very useful.

In looking at the different studies, I just wonder whether one could not construct an ROC curve over the totality of data in some way. I don't know, maybe somebody wants to comment from a statistical perspective on that, or whether you do. But I would like to somehow be able to summarize everything we know.

DR. RACZKOWSKI: In my review, I did reference a recent pooled analysis that was published I think in the Journal of the American College of Cardiology in about 1998 or so which covered many of the same articles. They, in fact, did do a pooled analysis. I ended up not including some of the studies that were included there because I felt that the quality of the studies didn't merit being included.

The issue of a meta-analysis is a much larger issue. And I do agree that there are a lot of similar things across the different studies, including endpoints, that potentially would lend itself to that sort of analysis.

DR. KONSTAM: Well, I guess, just listening to your presentation, I'm left with a lot of questions about exactly what do we think is the sensitivity and specificity, about what are the correct or optimal diagnostic criteria that should be applied to the studies to get the most out of them. If I'm a clinician and I'm

looking to the FDA to an approval here, I guess I would like some help about that. And I don't get it from looking at all the individual studies in isolation.

I don't know if Dr. Maddahi wants to comment on that.

DR. MADDAHI: I agree that meta-analysis or pooled literature has some advantages. But knowing some of the difficulties also, it is that you're dealing with some studies that are not exactly uniform. If it would be helpful to the panel and to Dr. Raczkowski, I have done a recent rerun of that pooled data with emphasis or special attention to the differences of some of the studies and how they were done that I would be glad to get a copy of that for the panel; either today or later I can submit that to the panel. I could actually ask my office to fax me a simple table of the average sensitivity or mean sensitivity and specificity that would help along those lines.

But what we've found is that the sensitivity and specificity are positive and negative to the predictive values are in the range of 82-83 percent with this technique, that is quite good, looking at regional wall motion. And we do have some other data for ventricular function improvement. I would be glad to provide that data.

DR. RACZKOWSKI: I think that would be great.

One of the issues that I struggled with is the definition of segment is different in all the patients. And given that difference, especially when the segments may not be mutually exclusive of one another in all the papers, how do you then go about pooling those data?

DR. MADDAHI: Right. I think that the point is that if the segments are very, very small, then I think that it is going to create a problem. And in fact, that would result into -- it has one advantage in that it provides more data for the investigator, but, on the other hand, it makes the misalignment of the segments between the various techniques much more difficult. So I think what you are saying is absolutely correct.

I think there is also other data, as you know, looking at ejection fraction changes, that is perhaps a better marker I think, and also prognosis. There are about four or five studies that, again, have been alluded to by you in some other literature that will be appearing later on this afternoon about the prognostic aspects also, several publications along those lines. So I think that if you look at four endpoints -- one being segmental wall motion improvement, the second being ejection fraction improvement, third being improvement of patient symptoms, heart failure symptoms, and fourth being improvement of patient survival and prognosis -- I think that among all of

those we can get a common theme here that would help a clinician as to where this technique might be helpful.

DR. TULCHINSKY: I would like to mention to the panel members that in Volume 3, the first reference is on that very specific topic. It is a meta-analysis. It was published in the New England Journal of Medicine, a very reputable publication source, and by very reputable people. They do cite all different tests and their sensitivity and specificity.

I also would like to comment on Dr. Raczkowski's compilation. It has been exclusively well-done given the problems we are addressing at the moment, especially the segments being difficult to follow. The first article that you have brought to our attention, Dr. Baer's article, which kind of strikes funny for Dr. Baer to talk about hibernation.

(Laughter.)

DR. TULCHINSKY: But I also notice that if you look at his drawings of segments, we in America usually refer to anterior walls and to the wall opposite as inferior wall, but Germans, being very logical, they term it posterior wall as contra distinction to anterior wall. And it is sometimes very difficult to follow those different nomenclatures.

In addition, you were talking about 50 percent

above the maximal pixel as being a criteria that they used. Now, for a moment, if one would think about it, 50 percent of maximal pixel activity, it is kind of like saying I jump about 50 percent in this room above the level of the ceiling, which is clearly impossible unless you have a pretty hard head, which many have posed to me as a possibility in my case. But in any event, what the authors probably meant is a 50 percent above the mean pixel count. But the way it came out seems to me to be a little different.

Jon, do you know something different?

DR. LINKS: It's 50 percent or greater of the maximal pixel count.

DR. TULCHINSKY: But the maximal -- you can't get 50 percent above the maximum, can you?

DR. LINKS: No, 50 percent of half of it or greater.

DR. TULCHINSKY: That's not how the sentence reads. But I think it is a translation difficulty though.

DR. RAMSEY: Any more questions or comments? That's what happens when you read these things here.

(Laughter.)

DR. RAMSEY: Okay. Seeing no further questions at the moment, why don't we proceed ahead with the next portion of our program.

DR. HOUN: We were thinking that maybe we should vote on the FDG question, then we can move on so that each drug product is fresh in people's minds.

DR. RAMSEY: Oh, my goodness, a vote here.

(Laughter.)

DR. RAMSEY: Okay.

DR. MADOO: Let me reiterate that apparently we have 12 eligible voters. Our guest experts, sadly, will not be voting. But our two august consultants from other committees will be contributing. Of course, the options are affirmative, negative, or abstain.

DR. KONSTAM: What did you just say, Leander?

(Laughter.)

DR. MADOO: What I'm saying is that apparently we're proceeding into the voting component of --

DR. KONSTAM: Who votes and who doesn't? I don't get it.

DR. MADOO: You as a consultant are eligible to vote.

DR. KONSTAM: I am eligible to vote.

DR. RAMSEY: I think Mr. Madoo is also making a point that there are 12, so there could be a tie.

DR. MADOO: It's conceivable.

DR. KONSTAM: I don't think that's going to happen.

Could we have a little more discussion before the vote? I don't know how you want to do it, Ruth.

DR. RAMSEY: If you feel like discussing it, I think we should do that.

DR. KONSTAM: I would just like to hear a little bit more discussion around the oncology indication. The issue about the diversity of the different studies and then merging them into a single indication, there really are two studies that you're really very happy with, those two are different, each one of them has problems. We're going to say it is for cancer. I don't know, do we need a little bit more discussion about what -- is there going to be actually a packet insert here, is that what happens? -- what the packet insert is going to say about this, which cancers. I would like to hear more discussion about this.

DR. HOUN: The way that this is being proposed, and that's why I'm very interested in hearing the discussion, is to have this broad indication to help in the evaluation of malignancy through identifying areas of abnormal glucose metabolism. We were not thinking of having a specific indication in terms of evaluating malignancy to identify lymphoma, or hepatic metastases, or small cell lung cancer. We were not going to specifically indicate the names of the cancers that the studies came from in the indication section.

However, in the clinical trials description part of the package insert, we are going to have the package insert for labeling for these products, we would describe the literature that was reviewed in terms of prospective studies, the number of patients all together, as well as the different types of cancers that these studies included. I know some of the folks in the PET community were interested in getting more specific cancers in the clinical trials section, such as brain tumors. But we didn't find, at least we weren't able to locate studies that were of a prospective nature, that had at least 50 evaluable patients, et cetera, et cetera. So in the clinical trials section of the label, we were going to discuss some of the criteria that brought the studies into the review of this process.

DR. KONSTAM: Well, maybe it's just because I don't know anything about this field, but I just am uncomfortable about this because I'm looking to the packet insert to give me guidance on how to use this agent. I understand there are people in the audience with a lot of experience and people with a lot of experience who just want to be able to use the agent. But the indication is going to be data-driven and the data are very diverse.

I just continue to be uncomfortable about an indication section that simply says diagnosis of

malignancies without any kind of data-driven information or conclusions around what are the cancers where we're confident, what are the cancers where we're not confident or we don't have any data. I don't know how the clinician is really going to be guided without that.

DR. HOUN: I'll ask for other members to help give FDA some direction. I do think we need to state in the labeling that using PET is not a substitute for other diagnostic, for biopsy, and that we need to caution in terms of false-negatives and false-positives do occur with PET scanning. But I'm interested in hearing the panel's views on how to handle this and what kinds of information doctors should be provided from the labeling to help them.

DR. LINKS: Jon Links. I like the proposed indication. The reason I like it is because it really represents, in terms of diagnostic imaging agents, the first attempt to move beyond the concept of diagnostic accuracy, per se, simple concepts of sensitivity and specificity, and to really acknowledge that in many nuclear medicine studies what you're trying to do is a functional characterization but in the setting of different diseases. Now there's a challenge in that, and the challenge is that we seem, certainly within nuclear medicine, and certainly today in the studies that have been presented, to always fall back on sensitivity and specificity. How are we to

move beyond sensitivity and specificity and diagnostic accuracy if we keep falling back on those?

The reason I like the indication is because it is a step away from simply looking at diagnostic accuracy. It is certainly true that this morning we were not presented with any data, to use your term, on the accuracy of quantification of glucose metabolic rate in a given lesion. But we know from other studies that we can accurately quantify metabolic rate.

Here's my point. My point is that the indication is not an indication focused on sensitivity and specificity, but rather on characterization when the presence of a lesion is already known. That is the way the indication is written. I favor it because that's what I think in clinical practice in oncology this agent is all about.

DR. MALCOLM: Arnold Malcolm. I totally agree with what Jon just said. We deal with this on a daily basis. It is the same situation we have -- in fact, I've never looked at a label for tecnesium for bone scans for patients; I don't even know what it says. But I know when a patient gets a bone scan and I have all the clinical information, I can make a clinical decision from that bone scan with tecnesium. And I think we're talking about the same situation again here. Maybe I'm simplifying it, I

don't know.

The studies that have been reviewed have talked about a variety of malignant diseases. And if you try to pick it through, it just won't happen.

DR. KONSTAM: Well, I don't know. I think people are bringing their own experience to the table, and that's always helpful. I wasn't necessarily talking about identifying sensitivities and specificities. It is one thing to say this thing is indicated, I have experience, I'm going to use it. It is another thing to say the FDA is going to declare that it is effective. And if the FDA is going to declare it is effective, to my way of thinking, I don't think it is so unreasonable to take a stab at asking what are the data to drive that, and where is the data in terms of what entities have been studies, what entities haven't been studied.

I've heard comments to the effect that there are certain cancers that just don't pick this up -- renal cell, if I'm not mistaken, for an example. Now, do you want that nowhere referenced? Is it sufficient to tell the clinician it is indicated for the diagnosis of malignancies without some comment about the fact that there are clear discrepancies across the different cancers? I'm not understanding.

DR. MALCOLM: I understand what you're saying.

I thought Dr. Houn was saying that the label would indicate which studies are being referenced for the disease type. I thought that's what I heard her say. Is that clear?

DR. HOUN: Yes. The comments I made in terms of saying some cancers are less likely to be picked up by PET, including bronchial alveolar carcinoma, low grade non-Hodgkin's lymphoma, those are general comments that come from the literature but there is no study on the specific entity showing PET performance is less. And so in that case, there is no data, except I guess there must be in terms of investigator experience and some --

DR. KONSTAM: Maybe we're going to be in a quandary. But, I'm sorry, I just can't get away from the fact that what we I think are supposed to do around this table is act upon data. That's all I'm saying.

DR. PONTO: Laura Ponto, University of Iowa. I think we're going back to the problems that we have had with indications that we've been struggling with as a committee for a couple of years now. Are we looking at a disease-specific indication, or are we looking at an imaging mechanism that tells us something about biochemistry. And the indication that I'm seeing here is that we are looking at glucose metabolism, and we know that in a large number of tumor types, because of their general metabolic activity, that glucose metabolism will be

"abnormal," and that that information then can tell the clinician where metastatic disease may exist, maybe give them prognostic information about the type of cancer that they are dealing with.

If we have the indication, as we are looking at glucose metabolism, then I think that we have the data that tells us, basic science data that says this agent gives us a picture of glucose metabolism. We know that tumors will have differences in glucose metabolism. And if that is the indication, we can make labeling changes that say certain types of cancers do not have large metabolic differences from normal tissue.

So I think that we're dealing with what is the indication, and the question is, is this effective for that indication? If we're going with a specific type of cancer, is it good in lung cancer, in melanoma, or whatever, we do not have the data here to possibly get that specific a type of indication. But a general, does FDG give us a picture of glucose metabolism in the body, and is it efficacious for that indication? That is I think what we're trying to deal with today, and that is what I think this indication is trying to get at. It may not be the correct wording altogether, but I think it is probably the correct one, at least in the ballpark.

DR. TULCHINSKY: Yes, I would like to echo that

comment. I totally agree with your assessment. Again, just as a basic reference, going back to what we have been through and said and done, I brought a book with me of package inserts. It's just my fun time reading before I go to bed.

(Laughter.)

DR. TULCHINSKY: I was looking at the indications for the bone-seeking radiopharmaceutical, the bone scan agent. Let me read it to you. "Technetium-99m metronate injection may be used as a bone imaging agent to delineate areas of altered osteogenesis." I suggest we keep those historical pieces in mind as we go forth here.

Also, I have to say that I disagree that we're not acting upon the data. I think we're very much acting upon the data. If it is not, what is the reference book that I'm holding right under my left arm? It's full of data. And it is not simply our personal experiences. I have to say I personally have no PET experience, so I don't have that. But we are looking at a compilation of literature experience. This is something that has been published, and most of it in very, very well peer-reviewed publications. Credibility ought to be given to that.

And I totally agree with the FDA's assessment for the labeling indication. I'm perfectly happy with it. Going back for a moment to the bone tracer, we all know

that the bone scan is less sensitive in patients with multiple myeloma. And that is not in the indication that it is less sensitive in multiple myeloma. I'm not sure it belongs there. It belongs in a text book. And we practice medicine not by package insert, we practice it by compilation of the textbook and our collegial and personal experience. So I would suggest we keep that in the background as a framework as we move forward.

DR. PONTO: To follow up my comment, I work in a PET center and I firmly believe in what I do. I think there is evidence that says that this is an incredibly useful technology. But I'm saying that in the two studies that were cited here, I can see where some people around this table would say this is not up to the same level that we're used to approving an indication for. But if we look at the literature as a whole, not only the disease-specific literature but malignancy as a whole, as well as the basic science literature, there is data that says that this agent gives us a picture of metabolism.

DR. TULCHINSKY: Again, I totally agree. I think we came prepared for this meeting to look at it in that particular way. That's why it makes it different. So I totally agree with you.

DR. ZIESSMAN: Harvey Ziessman. I think that the medical community in general has been urging the FDA to

get away from the specific one drug, one diagnosis indication approach. And this is I think a major advance. We don't want the FDA to be telling us how to practice medicine. I doubt very much whether you look at the package insert to decide what the indications are for treating patients, because I know most physicians don't.

This is an approach that I think many have been urging on the FDA for some time. I think they are to be commended for it. And I'm in favor of it.

DR. KONSTAM: Can I respond to that? First of all, I would say that I disagree. I think that the FDA is very specifically here to tell us what are the data that support the practice of medicine. And if you as a clinician want to go beyond that, that's your prerogative; nobody is stopping you from doing that, the FDA isn't stopping you from doing that. The FDA hasn't been stopping us from using FDG for quite a while now.

But I specifically think the FDA has a major role to educate the clinician, to tell you, okay, what do the data show. This is proof, this is what we know about this. Now if you want to go beyond that, that's fine, but this is what we know about this.

Now I think this situation is odd. And we're going to resolve this. I think this agent needs to be approved and go beyond it. But I think it is odd because

everybody around the room knows there is no such thing as malignancy, that we're talking about an assortment of scores of diseases. And so I guess I have a very different reaction from people around the room. My reaction is that to not find some way to acknowledge that, and I'm not sure what the way is, but my feeling is to not find some way to acknowledge that in the written indication is as if to say all cancers are the same. And that's what I feel you're saying to the clinician. So I guess I have a very different interpretation.

DR. ZIESSMAN: But I don't think the purpose of the FDA is to educate, as you're saying. I think the purpose is to tell us that drug is safe and efficacious. And if it is, then it is up to the physician to use the drug appropriately.

DR. TATUM: Could I just suggest that maybe we change a little bit the verbiage to try to reflect the statement with the data that we have. And maybe just think about this, it is really a subtle change, "Detection of enhanced glucose metabolism associated with known or suspected malignant tumors," which after that could follow the statement that you would enclose. That would flow quite nicely. Just a suggestion.

DR. LINKS: I was going to suggest something similar. I strongly support that. Take, for example, a

tumor that may or may not express a certain receptor and you have a receptor imaging agent, and I'm predicting something that will probably come before this committee at some point, and if all you were to do is to ask the question, "What is the sensitivity and specificity of that receptor binding radiopharmaceutical?" In my opinion, it would be a grossly misleading kind of study because the point of using that radiopharmaceutical is not to detect the lesion but to characterize the lesion.

I think where we're getting sucked into this confusion and the fact that different types of tumors may or may not take up FDG to the same extent is because we're focusing again on the detection part. What we're really talking about here is assessment of glucose metabolism in lesions. And the way the indication is written here, it is known. I like your addition of "or suspected." But, quite frankly, the name of the game in this indication is not raw detection, per se. And the name of the game of FDG is not raw detection, per se, necessarily, but rather assessment of metabolism.

DR. TULCHINSKY: Would you consider also adding "and extent of the tumor." Because oftentimes once we characterize the lesion, we would like to also see if there are others. So I would wonder if that would be useful to incorporate. But, in general, I was, frankly, perfectly

happy with the way it was written in the beginning.

DR. HAMMES: Just a comment along these lines. From reading the indication as it is written, we're basically just saying that, yes, FDG can measure glucose metabolism, that it is known that some malignancies to a greater or less extent use more glucose, and hence, by extension, we can make some determinations clinically about that. But it is very clear to me that we're not operating in a static vacuum here. What we know about it in terms of cancers is going to change, and that is the practice of medicine. We expect our physicians to stay current with the current literature about what is known about things. And that doesn't belong in a package insert. I'm very happy with it as written.

DR. RAMSEY: Any other comments?

(No response.)

DR. RAMSEY: A suggestion has been made that we vote on these. And I guess that's appropriate then at this time. Is that then Questions 1 and 2. And this is in your handout. I numbered it as page 5.

DR. LINKS: We've now had recommendations for wording changes on both indications.

DR. RAMSEY: Would that come under discussion or --

DR. LINKS: I personally like most of the

wording changes I heard about for both indications. I would just as soon vote on the changed ones rather than the original ones.

DR. RAMSEY: Okay. All right. Let's go to Question 1. Question 1 is: Based upon the presented literature review, do you think fludeoxyglucose F-18 injection is safe and effective in positron emission tomography (PET) imaging for identification of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with abnormalities found by other testing modalities, or in patients with existing diagnosis of cancer?

That is the statement before us. And now if we want to modify it, why don't the modifiers suggest their modifications again.

DR. TATUM: Mine was to change it to "detection of enhanced glucose metabolism associated with known or suspected malignant tumors." I'm just replacing the original, not with a question.

DR. RAMSEY: Just a little slower.

DR. TATUM: Detection of enhanced glucose metabolism associated with known or suspected malignant tumors.

DR. KONSTAM: Can I just ask the FDA, just in terms of what -- I guess I'm not picturing what an

indication section of a packet insert looks like. In other words, this is the indication, but then there is a discussion within the indication. Can you comment?

DR. LOVE: The package insert generally, in relationship to what we're talking about, would have something called a clinical pharmacology section which would describe mechanism of action, pharmacokinetics, and what is known about the drug itself, a clinical trials section that would discuss the database essentially, the key studies usually, and then an indication section which is just a discreet one or two sentences most often.

DR. KONSTAM: So this would be the entirety of the indication section.

DR. LOVE: The indication section.

DR. ZIESSMAN: I would suggest that Jim's suggestion "detect," I would rather use the word "evaluate" or "assess," something rather than detect.

DR. RAMSEY: Dr. Tatum, would you accept that?

DR. TATUM: Yes.

DR. LINKS: And I would just as soon eliminate the word "enhanced." It is assessment of glucose metabolism.

DR. TATUM: That's what you do by changing detection to enhance, it becomes value.

DR. RAMSEY: Okay, I got lost there.

DR. MADOO: Would someone read the concrete new statement. I guess I'm experiencing abnormal glucose metabolism.

(Laughter.)

DR. RAMSEY: Start from PET imaging in line 2.

DR. LINKS: Okay. So I am modifying the questions for MIDAC, right?

DR. RAMSEY: Right.

DR. LINKS: So, is safe and effective in PET imaging for "assessment of glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with existing diagnosis of cancer."

DR. RAMSEY: Comments?

DR. KONSTAM: I don't suppose anybody would go for saying "certain cancers."

PARTICIPANT: No.

(Laughter.)

DR. PONTO: This may be opening an entire can of worms that we don't want to, but do we want to leave positron emission tomography in there since individuals are sometimes imaged using SPECT technology?

DR. HOUN: The data reviewed was for PET technology.

DR. TULCHINSKY: Since the technology is

evolving quickly, I don't see a very compelling reason to include that at all, frankly. Does anyone feel different?

DR. RAMSEY: Is that appropriate?

Yes, go ahead.

DR. CONTI: You can actually consider an imaging adjunct for the assessment and take out the specific technology.

DR. MADOO: Please identify yourself.

DR. CONTI: Peter Conti from USC. "Effective as an imaging adjunct for the assessment..." That's another possibility. And take out the word "PET."

DR. RAMSEY: Any other comments? But we are discussing PET, right? I think they want it in there.

DR. HOUN: I don't think you will get very far without us talking about PET, as mandated by Congress.

DR. RAMSEY: Okay. So, Dr. Conti, can we leave that in there?

DR. CONTI: That's fine with me.

DR. RAMSEY: Thank you.

Any other?

MS. BEAMAN: Carolyn Beaman, consumer representative. I think that we've stretched some things beyond their elasticity point already. And now if we go back and start trying to rename the method of imagery and on and on, then we might as well just make up a whole lot

of data, just make it up and play it by ear as we go. We can't reach in there and pull PET out like that, or we shouldn't.

DR. RAMSEY: I think it will be left in there. I think that's what we're talking about. That's what they want us to do. So, right now it is in there.

Any other questions?

(No response.)

DR. RAMSEY: Maybe we should read what we're voting on again. Who knows what we're reading here?

(Laughter.)

Jonathan?

DR. LINKS: Okay. So, F-18 FDG injection is safe and effective in positron emission tomography imaging for assessment of glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with existing diagnoses of cancer.

DR. RAMSEY: All right. That is what we're voting on then.

Mr. Madoo, would you help me verify whoever is eligible to vote here?

DR. MADOO: Certainly. Okay, again, the 12 eligible voters proceed.

DR. RAMSEY: Do we have to call for the

question here, or how do we do this?

DR. HOUN: We would appreciate also hearing from non-voting members their views. But that wouldn't be counted as a vote. Just to hear their views.

DR. RAMSEY: So before we vote, do we want to hear those views? Because it might change somebody's vote. I think they wanted comments from non-voting members, if anybody has any. Somehow I think this is not a shy group here.

DR. HOUN: If the non-voting members could comment whether they are supportive or not supportive, that would help us.

DR. RAMSEY: Okay. Why don't we just start with Dr. Herscovitch. And make a comment why you either support it or don't support it.

DR. HERSCOVITCH: I'm supportive of the question as amended. I still have reservation about the perhaps mismatch between the original question and the data, but that's perhaps a minor reservation because the ultimate issue is its use as a metabolic agent in the specific cases that have been very well documented both in the literature and by the FDA reviewers.

I think that it is important to realize that many of these tracers are physiologic tracers, and that it may be a bit of a mindset or a paradigm shift, to use

another cliche, but I think increasingly in the field of nuclear medicine, definitely in the field of PET, there are going to be tracers based on biochemical mechanisms not more physicochemical mechanisms.

And I think it is important for what we're doing today that we not only realize that we, or you, not me because I'm not voting, that you all are deciding on an indication, but also that you are establishing a process for how these agents, especially PET agents in the future, might be assessed. And in that regard, not being familiar with this process, I do have to give some credence to the views expressed by Dr. Konstam about the level of proof that is needed for these agents. But that aside, I would, if I were voting, vote in favor of this indication.

DR. TATUM: I obviously support the way it was amended. I think there are a couple of things I would like to say since I'm not voting that are important. Jonathan pointed out that this is probably the start of a process where we're going to be dealing with a number of agents in the future. And I don't think they are all just PET agents. As we begin to look at molecular probes, we're going to have this same problem. We're going to have things that do not have sponsors because they do not commercially have a large enough target audience, but yet they may have a very valuable asset to programs and to

development.

One of the things that is an issue at NCI right now is in mechanistic drug design and trying to get probes, and PET is one of the areas where it is difficult. And to get the number of clinical trials to answer the secondary questions you're coming up with, we really need more sources of these. And without approval, I think it is going to be extremely difficult.

So, again, I do support this. I do think you're setting a precedent that also is a slippery slope because it does in fact say how in the future these are going to be evaluated and tested. And maybe we should keep in mind that the data needs to look a little bit more like a regular commercial application in the future at the same time. So, I think it is important for this particular course, but it also sets a precedent for the future.

DR. KONSTAM: I probably shouldn't be allowed to vote because I don't know anything about this. But then, again, maybe I'm thinking that it's good to have somebody who doesn't know anything about it so he's forced to sort of make his decision purely based on the data that he's seeing. And I guess I'm going to hold out. I'm going to vote no to this. I think that it should be approved, even though I'm confused about what the standard is. But what the heck? It's been around for a long time. I do

believe it works based on looking at the totality of the data.

However, I just want to express my deep concern about an indication that talks about cancer as if it is some homogeneous process and where the data are sparse to absent to negative in some areas. And so what I would urge the FDA to do is simply amend whatever specific wording you're coming up with to include a term like certain malignancies, or certain cancers, or selected -- I guess that's the best way I can come up with it -- certain malignancies and certain cancers.

DR. MADOO: Dr. Konstam's vote duly recorded as a no.

MS. BEAMAN: Carolyn Beaman again. I think that it is clear that the FDG or PET can detect changes in glucose utilization patterns. I would, however, suggest that in the future when pharmaceuticals are brought before this or other similar committees that we definitely need a more detailed guideline for interpretation. I think that goes without saying. But having said that, I reluctantly support the question as amended.

DR. MADOO: Duly recorded as a yes.

DR. HAMMES: Richard Hammes, University of Wisconsin. I think by all accounts this has been shown to be about the safest drug ever considered. There has never

been an adverse effect reported, so we're only talking about efficacy. It has been well accepted for over 20 years in the nuclear medicine PET community as being a good marker of glucose metabolism, with some very thorough animal work to back that up.

The only reason that we're going through this strange process is because there hasn't been a sponsor, there hasn't been enough money, it hasn't been patentable. I don't think this necessarily should be the model for the future. I think the PET community needs to learn what kind of data would convince everybody who perhaps isn't an expert in the field out there and that is the kind of studies that need to be done in the future.

But this is an indication that needs to be approved. The people that can afford it have been getting it for 20 years. All we're doing is making it effectively available to the Medicare population, the Medicaid population, the poor population, and maybe allow them to get reimbursement support so that they can also benefit. I vote yes.

DR. HERTZBERG: Likewise, I vote yes, although I share some of the reservations about the specific concerns expressed about the disease entity. I don't know what disease entity it is being indicated for. But I do think that it is efficacious. I do think there are issues

with regard to patient preparation for the procedure that need to be cautioned about. But I do vote a yes.

DR. TULCHINSKY: I guess there is no suspense, my vote is yes. I have no reservations, frankly. I think we are not doing anything that is terribly unusual given other indications I've read through in the package inserts that I've gone through. I have to tell you that I do go through package inserts on everything that I use. I think there is a great deal of useful data in it and I respect that very much.

I think it is a milestone though that we have come upon because today we have used a bit more of scientific, logical thinking in synthesizing the data to support our yes for this particular vote, at least those who are voting yes. I think it is a step in the right direction.

DR. CHOYKE: I'm going to try to get the brevity award. I'll vote yes for all the reasons stated.

DR. MALCOLM: Bet you I can outdo you. My vote is yes.

DR. RAMSEY: I vote yes as well. I also concur with everything that has been said. I think this is something that is being used very commonly, although there are not as many PET scanners as there are CT scanners and MR scanners. I think if agents like this are approved, I

think we'll see the data that people have expressed some concerns about and it will allow us to go forth in a more widely and freely way to further evaluate this new agent.

DR. PONTO: I obviously also vote yes. I would like to urge the FDA though to write very detailed use instructions. Specifically, I would like to urge them to have patients monitored for their glucose levels, because I think that very importantly can impact the efficacy of a particular scan.

DR. AMENDOLA: I think that based on the evidence presented here, a little bit of my personal experience with this agent, my vote is a qualified yes. I share some of the reservations that were expressed. But I think this is a really valuable addition to the practice. So my vote is yes.

DR. ZIESSMAN: I think this radiopharmaceutical is clearly safe and effective. And I think this new approach is a major step forward. I don't agree that we ought to be closely monitoring glucose levels routinely, as you suggested. In fact, I think Dr. Coleman mentioned earlier that they do not check them routinely except under certain exceptions. And I don't think that ought to be part of the package insert, other than a comment that it may be indicated in some instances.

DR. LINKS: Yes.

(Laughter.)

DR. MADOO: I have the official vote tally. It appears to be 11 yes, 1 no. And I duly respect Dr. Konstam's viewpoint.

DR. RAMSEY: Thank you all.

I think there is Question 2 also under this agent. "Based upon the presented literature review, do you think fludeoxyglucose F-18 inject is safe and effective in positron emission tomography (PET) imaging in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging, to identify left ventricular myocardium with altered glucose metabolism and reversible loss of contractility?"

DR. KONSTAM: Could I just re-read my suggested change to that?

DR. RAMSEY: Please.

DR. KONSTAM: All the stuff you said at the beginning, Ruth, and then where it goes "to identify left ventricular myocardium," I've jotted down "to examine myocardial glucose metabolism and identify myocardium with reversible loss of systolic function," and then to continue, when used together with myocardial perfusion imaging, et cetera. So the two changes are just changing the word "contractility," and just taking out the "altered glucose metabolism" part.

DR. RAMSEY: Are there any comments on that suggested change?

(No response.)

DR. RAMSEY: In general, are there any comments or discussion? FDA, would anyone like to make any?

DR. ZIESSMAN: I'm in favor of that change.

DR. RAMSEY: Would you like the same thing again, a vote and comments. Are we prepared to vote then.

Why don't we use the same method again. Dr. Herscovitch, you can go first.

DR. HERSCOVITCH: I would vote in favor. I think this is a lot more clear-cut than some of the earlier discussions we were having. Perhaps one thing to clarify it. I think it is fairly obvious to everyone in the room that the myocardial perfusion imaging is not necessarily with the other PET agent N-13 ammonia, but other agents as well, more conventional agents. Because especially in some facilities, FDG will be available from other providers but the ammonia won't because of absence of an in-house cyclotron. So, I think just to make that clarification, although it was probably clear to everybody before I said that, in this room at least.

DR. TATUM: A straightforward yes on this one. Well supported, well documented.

DR. MADOO: Excuse me. Before we proceed with

the vote, some of us are experiencing Y2K problems. We would like to have the rephrasing of the question again. Read the question, please, the entire question.

DR. KONSTAM: Well, I don't have the beginning of it. Okay, I got it. "Based upon the presented literature review, do you think fludeoxyglucose F-18 injection is safe and effective in positron emission tomography (PET) imaging in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging" -- I'm sorry, the wording is just backwards. That's fine. So, "when used together with myocardial perfusion imaging, to examine myocardial glucose metabolism and to identify myocardium with reversible loss of systolic function."

Oh, yes. The only thing is I would urge the FDA I think to develop some kind of advice in the packet insert regarding what we think the true boundaries of sensitivity and specificity are with selected methodology, because I don't have a clear sense of that right now and I think it could use a little work.

DR. MADOO: So you vote yes I take it?

DR. KONSTAM: I vote yes.

MS. BEAMAN: Yes.

DR. HAMMES: Yes.

DR. HERTZBERG: Yes, again with the language

about appropriate patient preparation.

DR. TULCHINSKY: Yes, as modified.

DR. CHOYKE: Yes.

DR. MALCOLM: Yes, as modified.

DR. RAMSEY: Yes.

DR. PONTO: Yes.

DR. AMENDOLA: Yes, as modified.

DR. ZIESSMAN: Yes.

DR. LINKS: Yes.

DR. MADOO: It appears we have a sweep, 12-0.

DR. RAMSEY: Thank you all.

We will now move on in the agenda. The next agenda item is FDA presentation on safety and effectiveness of nitrogen N-13 Injection. Our first presenter I believe will be Dr. David G. Udo, Ph.D., on clinical pharmacology, pharmacology, and toxicology. Thank you.

Oh, a break? We have a question for a break here.

DR. MADOO: What time was the scheduled break? Is there a motion to have the break now, or would you like to proceed with all due purpose into the N-13 world? The committee requests a break. Dr. Ramsey, is that appropriate?

DR. RAMSEY: Yes. Let's take ten minutes, and we'll come back here at five minutes to the hour.