we changed the colonoscopy view to say, you know, is it picking up cancers? So it depends on the endpoint. But in any case, ROCs are relevant. Is that your view?

DR. SAMUELSON: Well actually, I'd like to hear your view at this point in time.

CHAIRMAN GLASSMAN: You will get your chance in a little while.

DR. SAMUELSON: Because that's what we're here for. I mean, I can give you my opinion, but actually that will differ from other people in the FDA, and I can tell you that. And it will differ from other people, well, a lot of other people.

So really, we're interested in your point of view, at this point in time.

CHAIRMAN GLASSMAN: Dr. Steier?

DR. STEIER: I have a question for Dr. Summers. What was mentioned was, in your presentation, was requiring a pre-read by the clinician in order to progress to the CAD component. Could you talk about that a little

bit more?

DR. SUMMERS: Right, I was trying to think about how we could avoid the slippage into the first read paradigm that was mentioned in the earlier talk about mammography and as a potential problem for the colon, also. And what came to mind was that, if the pre-CAD reading is recorded, it may not be in the published report that goes in the patient file, but it may be that in the future there will be auditing and accreditation similar for, to mammography accredited centers.

And so that information would be available to the auditor, and then you could see whether the physician's performance pre-CAD met certain guidelines, which of course, are unspecified at this time. But that would be the idea.

CHAIRMAN GLASSMAN: Dr. D'Orsi has a question.

DR. D'ORSI: For the person who

didn't feel ROC was relevant - I don't know who that, I forgot, I'm sorry - if you give -- I can understand the relevance if you are asking for cancer versus non-cancer. I can't understand if you give proper instructions for the presence or absence of a polyp. Maybe I'm missing something.

DR. BEDDOE: I have to apologize. I'm not a statistician myself, so I can't speak on the subtleties of this argument. That was presented by Steve Halligan, from UCH.

CHAIRMAN GLASSMAN: Thank you. Any other questions?

DR. ROSENBERG: One for Dr. Samuelson. Others might be able to -- analogizing CT colonography with mammography, it seems like the cut-point is whether the patient needs to go from the CT scan to colonoscopy.

DR. SAMUELSON: Okay.

DR. ROSENBERG: So, which is based

on number of polyps and accuracy of size measurement. So can that type of analysis be applicable to these devices?

DR. SAMUELSON: Which type of analysis? I'm sorry.

DR. ROSENBERG: Well, which category does the CAD device place the patient in? How accurately does the CAD device, with the assistance of the radiologist, and alone, accurately categorize the patient?

DR. SAMUELSON: I guess I'm not catching your question. In both cases, the CAD goes to the image, marks a number of different locations, and typically those numbers of locations is going to be on the order of two because that's the typical number of false positives per image – two, maybe three or four, something like that. And that happens in both cases, in both a CTC and a mammogram, that's what the CAD devices will do. And then it is up to the radiologist to go and eliminate and look at each of those

locations and eliminate them as possibilities of being actual lesions.

DR. ROSENBERG: Okay.

DR. SAMUELSON: And then it's up to the radiologist to make the decision as to whether to send that person on to optical colonoscopy, or send them on to, you know, further diagnostic imaging, or biopsy, or whatever in mammography.

DR. ROSENBERG: Okay.

DR. SAMUELSON: Does that make sense?

DR. ROSENBERG: Yes.

DR. SAMUELSON: Does that cover your question?

DR. ROSENBERG: That's fine.

DR. SAMUELSON: Okay, thanks.

CHAIRMAN GLASSMAN: Any other questions for any of our speakers? If not, we will now continue with the Panel's general discussion of colon CAD devices after which we will focus our deliberations on the specific

FDA questions.

I would like to remind the public observers of the meeting that, while this portion of the meeting is open to public observation, public attendees may not participate unless specifically requested to do so by the Chair.

I would like to begin the general discussion now. Dr. Wong, do you want to start?

DR. WONG: Yes, I do.

CHAIRMAN GLASSMAN: Colon CAD. Any general comments you want to make?

DR. WONG: Yes, I think that the actual colon CAD is really a major advance in the sense that it allows us to, without you know, a radiologist, identify major lesions in the colon. I think that as a practical gastroenterologist, or let me just put it this way, as a physician recognizing that colon cancer is a major problem and recognizing that basically, if you look at any form of testing

for colon cancer, if you do it, you have a major advantage in the sense that you actually identify lesions, you probably save lives. So I mean that's basic, and I think we all understand that.

So in one sense, this CAD system is really an advance. The problem is, that obviously, the question is, does it save you time? Because we always run into this problem with time. And that is, if you're doing a screening test, and generally speaking what I have seen at Walter Reed where we do a lot of CTCs, virtual colonoscopy, we do either of those, optical colonoscopy or CTC.

The patient can choose. We decided, at Walter Reed, at the Navy, where Pickhardt was located, Dr. Troy is located, that it's good enough, with the data that we have had from the New England Journal article, that we offer both of these tests to the patients.

That, when you get the CAD system,

what you are hoping for, is because you've got so many patients that you need to screen, you might be able to save some time. The unfortunate thing and the good thing about CAD is that you identify these, but you still need somebody to go over the CAD which means that the individual probably has to be a second reader, which means he has got to read the virtual colonoscopy, spend time doing that, then look at the CAD, read the CAD which will just add more time.

The hope would be that the CAD would be so good that it could actually be a primary reader, so you could move people through the system and you could do more patients. I mean, I think that's something that is sort of a utopian view.

On the other hand, you could look at it and say that the likelihood of a CAD missing a very large lesion, that is to say, greater than one centimeter, is probably small, and that in one sense, the CAD would

probably pick up the vast majority of patients, if you're looking at that as your ultimate criteria, greater than 10 millimeters, or one centimeter.

CHAIRMAN GLASSMAN: Okay. Dr. Swerdlow?

DR. SWERDLOW: I agree. I think one of the key differences between mammography and CTC is the length of time it takes to read one mammogram is much, much shorter than it takes to read a CTC. Dr. Kim has much more CTC experience than I do, but I'm still on the order of more than 20 minutes to read one. And you are probably faster.

But to have -- if the number of cases grows the way it has the potential to, we really do need some time saving. The other key point, I think, is that if the trigger is to trigger an action in mammography, to trigger a call back, or to trigger a biopsy, versus a CTC, it triggers a colonoscopy. If -- I think there is more of a first reader or

concurrent reader potential here because if it finds one polyp big enough, even if we don't quite catch all the polyps, that's going to trigger an action. And hopefully, the optical colonoscopy will catch them.

That said, if, as a first reader, it doesn't catch them, I think we still have to do a very careful detailed examination because you can't trust it. But there is some inherent differences such as that to think about when comparing this to a mammography system.

CHAIRMAN GLASSMAN: Dr. Kim?

DR. KIM: You know, I think CAD really will have an interesting and positive role in CT colonography. Just to give you a little bit of background, one of the reasons I think CT colonography is so effective at detecting polyps is the redundancy of the technique. So two series are acquired, prone and supine, and from those series we look at the data six times.

Basically two fly-throughs, rectum to cecum and cecum back to rectum for each series. And then we look at the 2D source data and look at a focused 2D in the areas that we know that 3D has some limitations, particularly in the aspect of carpet lesions in the cecum and rectum.

And so it's that redundancy that has allowed us to have high sensitivities. And I think that CAD is going to be very important to add a layer of redundancy, particularly if you use a 2D primary reader paradigm for CTC.

So one way is to look at the data 3D for polyp detection. The other way is to look predominantly at 2D. And I think that, you know, I really believe that the 3D is a more sensitive way to go, but it's probably likely that, as radiologists -- as this is rolled out, radiologists will start with the primary 2D because it's very familiar. It's essentially like reading a CT scan.

The problem with the primary 2D is that you have perceptual -- pure perceptual abnormalities where what you think is a fold, actually is a focal polyp. And when you turn to the 3D display, you realize in 3D that it's a focal polyp. And that's why you hear people from a primary 2D approach say they use primary 3D for characterization because they are looking at the 3D aspect of it.

So even for large lesions over a centimeter, unless you take a very meticulous search pattern and you're experienced, there is a possibility that you could miss that lesion. And that is the lesion I see as CAD -- no CAD system should miss that lesion. You have that extra layer of redundancy, kind of a spell checker in that instance.

And I think what we have to decide is where we're going to set the set point for CAD. I would argue that you should set it on the bigger side to make sure you don't miss the important lesions and not worry so much

about sub-centimeter lesions.

And then to get back to you on the point of how are things measured in the CTC literature, people have reported out per polyp set points in terms of sensitivity and specificities, per adenoma, and per patient. And we know that between per polyp and per adenoma because when you look at a polyp, you have no idea what the histology is. Is it hyperplastic mucosal, or adenomatous?

We know that if you look at per polyp, you are going to have a lower sensitivity at CTC for a given size than if you look at per adenoma. And the theory is that the non-neoplastic lesions, hyperplastic or mucosal, flatten out with CO_2 distension and become harder to see.

And so, you know, what we're doing is trying to find a surrogate for the target lesion, the benign -- and it's a benign lesion. And I think that's one of the things that sometimes gets lost in the shuffle.

We're not looking for cancer when we screen for colorectal cancer. We're looking for a benign precursor target lesion that will turn into cancer, and typically, that has been a small set, subset of adenomas, although with more recent information, there probably is a small subset of hyperplastic polyps that turn into cancer as well.

But the good thing is, we have this huge time interval and the fact that the cancer -- it usually takes a certain size before the majority of the cancers occur. And so we can use size as kind of our surrogate and our cut-point. And I would say that one of the discussion points would be where to set that, and I would say a centimeter would be a logical choice.

CHAIRMAN GLASSMAN: Let me ask Dr. Lin to comment, and then we'll open it up to the rest of the Panel.

DR. LIN: Thank you. I just want to make a few points about a few topics, areas

in which colon CAD may be different from mammography CAD. There was some comment about the use of ROC curve analysis. In my opinion, I don't think ROC curve analysis is needed in this situation because it's a little different from the situation with the breast.

Here we're really looking at a binary decision point. We are deciding whether or not the patient needs to go to colonoscopy. And all we have to do is, basically set a cutoff point, and people may disagree about the actual cutoff point. I think a lot of people would agree that a 6 millimeter polyp might be a reasonable cutoff point. But whatever that cutoff point is, we can set a cutoff point and then calculate a sensitivity and specificity without actually using ROC curve analysis, which is, I think, kind of cumbersome in this situation. So I think that's a major difference from mammography CAD.

The other issue has to do with what

to use for the so-called ground truth or gold standard test. And I think most gastroenterologists would agree that we should use the technique of segmental unblinding which basically combines information from both the optical colonoscopy as well as the virtual colonoscopy, to arrive at a gold standard.

The third point I wanted to make was for colonography studies, the prevalence of lesions of interest, which in this case, would probably be large polyps and colon cancer, that prevalence is relatively high. It's much higher than the prevalence for breast cancer, which is around 0.5 percent.

For colon cancer and large colon polyps, larger than one centimeter, it's around 5 percent. So in this kind of situation, there may not be a need for case enrichment. And we would be able to calculate sensitivity/specificity, as well as positive and negative predictive values, you know, when we don't image the database.

The other point I wanted to make is to agree with some of the other speakers, I think the CAD should be used as a -- in a second reader role, okay, to improve sensitivity of the colonography technology. I think we should focus on that instead of focusing on trying to reduce the reading time, because, right now, there is still -- I can tell you from the gastroenterology perspective, there is still some question as to the accuracy of CT colonography.

And I think any technique that we have available to improve the accuracy of CT colonography is going to be helpful, instead of trying to find ways to reduce reading time.

And then, the last quick thing I wanted to mention was the issue of overlap criteria. For the breast, I think it's relatively easy to see if a certain lesion that was seen in one imaging study, is actually another lesion that's seen in a different imaging study.

But in the colon, sometimes it's very difficult to figure out if a certain lesion that was seen on CT colonography is actually the same lesion that's seen on optical colonoscopy because the colon is very mobile. So it's not stationary like the breast is.

Not only is there an issue of the 3-dimensional, you know, question, but it actually moves around. So that is difficult when doing studies.

CHAIRMAN GLASSMAN: Are there any other comments from Members of the Panel about general CT colonography? Dr. D'Orsi?

DR. D'ORSI: I just wanted to get an idea of the number of people eligible for screening colon exam per year about.

DR. KIM: There is about 80 million people over the age of 50 that would be eligible for screening. And of that group, currently about 40 million individuals choose not to get screened. The 40 million that do

choose to get screened per year, about two million is done by optical colonoscopy, and the large segment is done by a non-full structure evaluation of the colon. So what we would consider is probably not the optimal way to look for polyps.

CHAIRMAN GLASSMAN: Dr. D'Orsi again.

DR. D'ORSI: Just a follow-up. If American Cancer Society information is disseminated and all of a sudden you had an influx of a very huge amount of people, do you have enough staff to handle that and do you think CAD would be helpful in alleviating that problem?

DR. KIM: Well, let me tackle this in two points. One is, is there enough staff, and is there enough hardware? The hardware question, we've looked at, and I think Perry has published this, and I can't remember the journal. But basically, we looked at whether or not there were enough current MDCT scanners

to handle this.

And we used a Markov model to look at how many scans you would need during a ramp-up phase, and then a steady state phase. And basically, the numbers that it came to with the current number of CT -- multi-detector CT scanners, by the IMD report, it would boil down to about 1.5 exams per scanner per day.

So I think on the hardware side, we certainly have the capacity to screen the people that need to be screened. The staffing side is another issue. If we can get enough people interested to do this because this really does require some specialized training to do, but hopefully we would be able to do it.

And I think as -- one of the reasons why I think CAD will be so effective is that, as people read studies away from the situation, the academic situation where you have a lot of time to look at cases, and you

are doing high volume screening, it's very hard to do from a 2D approach. And if you tried to do it, I think that CAD will be something that you would really want to use as a something like a -- that checks your -- checks to make sure that you haven't made an error because you've gone too fast and missed a big polyp.

CHAIRMAN GLASSMAN: Any other general comments? Dr. Dodd?

DR. DODD: I just want to ask Dr. Lin a question relating to the ROC analysis. I understand that you want to set some threshold of, you know, say greater than a centimeter at a minimum, but is it not possible to assign some likelihood of that polyp being greater than a certain size?

DR. LIN: I think it's certainly possible. I just don't think it's really necessary because, you know, when the radiologist reads the virtual colonoscopy scan, they basically report a size. They say

they think this is eight millimeters. I'm not sure how they can score how likely that this assessment is accurate. Maybe Dr. Kim can comment on that.

DR. KIM: Well, I think that, actually, we do score likelihood in terms of likelihood of it being a true soft-tissue polyp. And so there is a classification scheme that we use, Walter Reed and Bethesda Naval used, as well, and that's the C-RADS classification.

The C-RADS document was drafted by the working group on virtual colonoscopy, and Mike Zalis was the lead author. And within C-RADS, there is a diagnostic score that ranges from one to three whether or not you truly believe what you are calling as a polyp is a true soft-tissue polyp. One being the least; three being the most certain.

And so I wonder if you can't do an ROC analysis from that because I can tell you, what happens infrequently is that we will call

a 15 millimeter polyp that is not seen, and it becomes a discordant case. And if our diagnostic score is three, all of those have turned out to be real because we call the patients back. They are on the second CTC. They go back to optical colonoscopy, and it's found.

If your diagnostic confidence is two or one, then the likelihood of it being real and repeat CTC or OC is much lower. So we actually do score all our polyps with this scale.

CHAIRMAN GLASSMAN: Okay. Dr. Berry?

DR. BERRY: A couple of points. First, Dr. Kim, I think you did not mean to say 40 million per year, because those who get screened regularly don't do it, and so probably eight million a year, or something like that.

The distinction between breast and colon; there has been a lot of studies that

address false positive in breast, and it's a period, and it's an indication that is very anxiety-ridden for women. It's a horrible circumstance at least temporarily.

Whereas in colon cancer, I don't know of studies, but I know of friends who say, you know, they found some polyps, and they took it out and it's -- you know, isn't that great? So I think the sensitivity issue is paramount, and I think this is consistent with what Dr. Kim indicated.

And that the false positive rate, if by false positive we mean we didn't find a polyp that was as big as we thought it was, is not that important. And so I think that's a distinction between the two in terms of sensitivity and specificity in the tradeoff.

With respect to that, ROCs, you know, ROC looks like a curve and, indeed, it is, but it's based on a sequence of yes or no, positive/negative, what do you call. So it's a dichotomous result.

Here in colorectal cancer, I'm not sure it's dichotomous. For example, suppose you define a true positive as a polyp that is six millimeters or greater, and your CAD leads you to do a colonoscopy, and you take the thing out, and it turns out to be five millimeters. Is that a false positive?

I mean, by your definition, it is, but I think some sort of -- I mean, maybe the dichotomous view of the ROC is not appropriate, and we ought to have some sort of category or, you know, continuum.

CHAIRMAN GLASSMAN: Dr. Garra?

DR. GARRA: I would just like to comment on the ROC thing. You know, if you were saying it was a six millimeter polyp, the rating scale would be how confident are you that it's six millimeters if you wanted to do measurements. But more likely, it's what Dr. Kim says, how confident are you that it is truly a polyp that is six millimeters in size versus some other kind of bump on the colon.

So this is a made-to-order category -- this is a made-to-order scheme that ROC can be used in. It's a detection experiment. It works perfectly in ROC, as far as I can see.

CHAIRMAN GLASSMAN: Okay.

DR. TOURASSI: I'm shifting gears a bit, but could somebody comment on any studies regarding the variability of radiologist's performance when interpreting CTC, in terms of sensitivity and specificity?

DR. KIM: Sure.

DR. TOURASSI: Is there a difference in terms of experience level -- Definitely size of polyps, and do you see a need for CAD to bridge the gap between less experienced radiologist and more experienced?

DR. KIM: In terms of CTC performance, I think the feasibility was shown pretty well by Helen Fenlon and Judy Yee. Helen Fenlon had a New England Journal article in 1999, and Judy Yee had an article in Radiology in 2001. Both series showed that,

at the 10 millimeter threshold, the sensitivity was over 90 percent.

A couple of years later, there were a series of four studies that kind of threw everything in disarray. Dan Johnson came out with a study that showed sensitivities at that 10 millimeter threshold of somewhere in the 50 to 60 percent. That was followed by Perry's study in the DOD trial in New England Journal, which showed for adenomatous polyps, it was at 93 percent, a little bit higher than 93 percent.

And then, on the heels of Perry's study were two studies, one by Don Rockey and the other by Peter Cotton, which again showed very poor sensitivities at 50 to 60 percent. And so people asked, you know, what is truly the performance of CTC, and I think that's what Otto was talking about, that people had questions about it.

And I think what people pointing to was multi-factorial. I would say one of the

largest contributors is this issue of 2D versus 3D, in that there are just some pure perceptual errors that you can do at 2D unless you really take care where they are much easier to detect as truly a polyp at 3D.

The other issues were related to the other aspects of the exam. They used older techniques, didn't fully distend the colon, did not use any oral tagging agents, and then there were some issues of reader training whether it was really not adequate training on this modality before the readers took part in the study.

I think now -- sorry, let -- just recently, there is now a consensus that CTC has sensitivities in 90 percent, ACRIN 6664, the Italian Colorectal Cancer Prevention Trial. The sensitivities probably are over 90 percent at the 10 millimeter threshold with state of the art technique.

DR. TOURASSI: So there is no issue regarding expertise, levels of expertise

because of that?

DR. KIM: I would say that if you are appropriately trained, that there isn't. But reader training is key because the ACRIN has shown that, if you aren't trained well, that you're going to miss it. So when they had called all the experts in to become readers, they had them take a competency test, and four failed. Actually, only nine passed, 11 failed, four of the 11 failed so badly that they decided not to be included, or something like that in the trial.

CHAIRMAN GLASSMAN: Okay. I want to move on to the questions, at this point. We have seven colon CAD questions, not CTC questions, but colon CAD questions. And I would like to focus on that now before we get a chance to leave this room.

So we're going to start with question C1, please. Please discuss the potential clinical utility of CTC colon CAD, including improved sensitivity to detection of

polyps of different sizes, reduced reading times, and guiding optical colonoscopy for intervention.

Why don't we -- we have touched on this, but why don't we look at this specifically right now, and why don't we have Dr. Swerdlow, Kim and Lin begin the discussion, and Dr. Wong, also. Who wants to go first? Dr. Kim? Great.

DR. KIM: You know, I guess, starting with the second one, reducing reading times. I think that for all the reasons, that it should be a second reader paradigm, and I can't see how that will reduce reading time. So add it, and hopefully it will be an acceptable amount.

In terms of guiding optical colonoscopy, I think that's more a function of CT colonography, whether you see it from a CAD mark, or whether the radiologist detected. It's the underlying CT colonography exam that will be able to guide exactly where the polyp

is.

In terms of improved sensitivities, different sizes, I think the biggest impact it's going to make from a public health standpoint, is that, if you set it at the 10 millimeter threshold, you're going to capture the lesions that really make a difference. You know, there is a lot of controversy with this six to nine millimeter group. And whether we drop it to 6 millimeters, you know, I think that's okay, but that is going to add to the number of false positives that you have to work through, and the number of CAD hits.

I think for certain that we should say that you can -- that it should not be intended for anything diminutive, that is, five millimeters or less.

DR. SWERDLOW: I essentially want to agree. Just to clarify, I think that, at this point, we're still relatively early in the game in terms of big numbers. The patients that -- clearly, we need to, you

know, make sure that our sensitivity numbers are absolutely solid and acting as a second reader is clearly the way to go.

When I was talking about improving reading times, I was really crystal balling way down into the future when, as we have discussed now, the potential for the number of patients can be potentially huge. But I think we are a long way from being to that point.

And I agree also the -- as far as guiding optical colonoscopy, that's essentially inherent in most of the software that is out there, regardless of whether the computer makes the mark or the radiologist.

CHAIRMAN GLASSMAN: What do you think about setting the equipment at 10 millimeters? You had mentioned, I think, six earlier.

DR. LIN: Yes, I think from a GI perspective, most gastroenterologists, actually I personally am a little ambivalent about that, but most gastroenterologists are

going to be uncomfortable setting the threshold at 10 millimeters.

10 millimeters is what we call an advanced neoplastic lesion by definition. And those lesions in GI studies are used as a surrogate endpoint as representing lesions where there is a high chance of progressing to colon cancer over the space of a few years.

Lesions that are six to nine millimeters in size usually are benign. There are -- there is a small percentage of them that actually harbor characteristics, like a high grade dysplasia or other histologic characteristics, that might make them higher risk.

So I don't know if most gastroenterologists are going to be comfortable excluding those lesions or disregarding those lesions.

So I think there is a sort of a different philosophy between GI and radiology when it comes to this sort of intermediate

sized group of polyps. And I would agree that polyps smaller than five millimeters are probably clinically not significant. And, in fact, studies have looked at that and the risk of colon cancer development is very small.

With regard to the questions, I would agree with Dr. Kim completely. The main purpose, I think, for the CAD is to improve sensitivity, not to reduce the reading time, at least at this point in time, at this point in its development.

And with regard to guiding optical colonoscopy, that's really going to be regardless of whether or not the lesion is found by CAD or by the radiologist. I mean, the colonography will be helpful in terms of guiding optical colonoscopy either way.

CHAIRMAN GLASSMAN: Dr. Wong?

DR. WONG: Yes, the only thing I would add is that what we find and what we've got to realize is, it's not just the gastroenterologist that sees these cases or

orders the CT. Ultimately, by doing virtual colonoscopy will open it to all various types of specialties.

So the family practice individual, they are the ones that are sending actually a large majority of the cases. So what happens is that a lot of this data that comes back in this area between 6 and 9 where there is a difference between the gastroenterologist and the radiologist, the primary care individual basically reads the results of the CT radiographer.

And right now, we have differing opinions. The CT radiographers bring patients back more frequently than we would, and obviously when we do it, we actually take the polyp out so the patient doesn't have to come back. So these are kind of just a little bit of the differences between the radiologist point of view at this point in time versus the gastroenterologist.

I think most gastroenterologists,

if they see a CT like we do, and we have a polyp between 6 and 9 millimeters, we tend to go ahead and offer the patient a colonoscopy, and you know, probably take the polyp out.

I think the primary care individual -- at Walter Reed, we tend to say you can come back in a year or in three years, depending on the size of the polyp. And the primary care individual will take the recommendations of the radiologist and follow it that way.

So I think there is just kind of a difference in opinion right now. I think the radiology community is probably a lot more cautious. They want to make sure that they follow the patients more carefully because we don't know what the endpoint is going to be. We don't have long-term studies.

But I think we all agree that a 1 millimeter -- one centimeter or 10 millimeter polyp is clearly the polyp that needs to be removed.

(Whereupon, at 5:00 p.m. the

meeting continued into the evening session.)

E-V-E-N-I-N-G S-E-S-S-I-O-N

5:00 p.m.

CHAIRMAN GLASSMAN: Dr. Swerdlow, any comment?

DR. SWERDLOW: Same points.

CHAIRMAN GLASSMAN: Same points. Well, I would like to ask a question, at this point. Dr. Lin, you mentioned that a 10 millimeter polyp was an advanced lesion which would turn into carcinoma within several years, if I'm quoting you correctly. If we have that kind of time, 10 millimeters, nine

millimeters, eight millimeters with follow-up, is that a reasonable thing from the gastroenterology standpoint?

DR. LIN: Well, I'm not sure. I don't think we really know what happens to these 1 centimeter polyps. I think the fear is that based on the studies that were done a long time ago when the natural history of polyps were followed because now a days we really can't do these studies. Whenever we see a one centimeter polyp, it's coming out.

So nobody really knows what the natural, the true natural history of the so-called advanced neoplasms are.

CHAIRMAN GLASSMAN: I guess I asked the question poorly. I really meant is it unreasonable to set the marker at 10 millimeters if we have time to find the six to nine millimeter two or three years later? That's really what I meant. I'm sorry.

DR. LIN: I guess that might be reasonable from a standpoint, but then the

question will be why not remove it now if we have to do another test in two or three years and probably will have to remove it at that time anyway? So but I can see what your point is, you know.

DR. KIM: I guess I would, if I could respond to that?

CHAIRMAN GLASSMAN: Sure.

DR. KIM: You know, I guess the problem that we have had with this argument, in one form or another between radiology and gastroenterology, and the reason why is, that screening by CTC is different from optical colonoscopy.

Optical colonoscopy; you are there and you see a polyp. It takes nothing to remove it. You have diagnostic and therapeutic options, and then so if you left it in to surveillance say, you know, it doesn't mean the size threshold is for following, and you send him back and see him back in two years. One, you don't know if it

has changed because it's very difficult for you to know if your sizes are reproducible at optical colonoscopy. And two, you don't know exactly where you are in the colon in terms of lesion localization.

So is that the same polyp or not? So it makes complete sense to clear out the colon. If you are screening by optical colonoscopy, you have a method of removing the polyps. What we are doing at CT colonography is one step removed from the therapeutic option. So it makes complete sense that if you had a huge population of low risk patients, you should filter them out and only send the ones that have a reasonable chance of having that benign precursor target.

And we're doing that by setting a size threshold. So, that's sort of the difference between the two philosophies. And I would agree with you that, you know, the 10 millimeter threshold and if it's an adenoma, it automatically makes it an advanced adenoma.

But a large portion of those are two vertices in histology. And I would say that that is a very different sort of biologic activity than something with high grade dysplasia.

So I think that the time interval you had, even for the 10 millimeter threshold, which we would all agree to get -- to send away to optical colonoscopy, that you have time. You know, there are studies that model that this may take, even for advanced lesion, up to five years plus.

CHAIRMAN GLASSMAN: Another question that I have. In your experience, those of you who do CT colonography CAD, has the CAD improved your sensitivity for polyps in a clinically relevant range? It's one of our specific questions, and I want to make sure that we get a specific answer to that.

DR. LIN: I have not used CAD.

CHAIRMAN GLASSMAN: Okay.

DR. KIM: We actually do not use CAD clinically. Our sensitivities have been

such at 90 percent for that 10 millimeter threshold that we actually do not use it as part of our clinical practice. So it's mostly just research.

CHAIRMAN GLASSMAN: How about in the literature? What are you aware of, either of you, or anyone else on the panel for that matter?

DR. BERRY: Mr. Chairman, can I point to the question which says, "identify potential".

It doesn't say we're supposed to answer the question, "is it sensitive?" Is this a potential benefit?

CHAIRMAN GLASSMAN: True. But if there is data out there that's known to answer it, but you're right.

DR. BERRY: Right.

CHAIRMAN GLASSMAN: Does anybody know of any studies?

DR. KIM: Well, Petrick's, Nicholas Petrick's study showed that, you know, for

size category six, nine and 10 millimeters above, that you're going to get somewhere between 14 or 15 percent increase in sensitivity for concomitant decrease in specificity. So although there was some trending, I think, to improving the area under the curve it wasn't statistically significant.

My guess is though that CAD will have a positive effect because of this redundancy adding another layer, another chance to detect a large polyp.

CHAIRMAN GLASSMAN: Any other comments? Dr. D'Orsi?

DR. D'ORSI: Let's say you are sent in by CAD or virtual, the CT colonoscopy to do an optical colonoscopy, and you see the large polyp, but you also see four five millimeter polyps. Do you clinically remove all of those or just the large one? And if you do remove all of them, will CAD, if it correctly identifies many five millimeter polyps, will that change the way you work clinically?

DR. WONG: Yes, I can answer that.

CHAIRMAN GLASSMAN: Good.

DR. WONG: When you do colonoscopy, you take everything out. You clean the colon. So while you have a larger polyp, any of the smaller polyps you would also remove.

DR. D'ORSI: Would you without -- CAD showed you four five millimeter polyps, would you go in and take all of those out?

DR. WONG: Well, generally, the way they read the virtual colonoscopy, anything less than five millimeters, they don't report.

DR. D'ORSI: But if you see them, because you're going in for something else, you will take them out?

DR. WONG: Oh, yes, yes, we will take everything out.

DR. D'ORSI: All right. Well, I'm a little confused.

DR. WONG: But I mean, we -- if you're looking at the criteria that are being used, you know, we -- they tell us the size of

the polyp and the ones that they send to us are greater than 10 millimeters. So those are the polyps -- those are the cases that we are doing related to virtual colonoscopy.

So in other words, if they report that there is less -- there is no evidence of anything less than five millimeters, we wouldn't do that. The other interesting thing that I should bring up is that when you see a larger size polyp on virtual colonoscopy, it's kind of our experience that these individuals may actually be polyp growers so that you may also maybe in 30 or 40 percent of the cases find more polyps than are actually noted on the VC.

So it's kind of a surrogate marker that this individual actually is a polyp grower. So in a sense, it's good for us because when we go in and find other polyps that may not be identified or even smaller ones, but several of them, I think we do a good thing for the patient.

CHAIRMAN GLASSMAN: Dr. Berry.

DR. BERRY: So can I ask a follow-up? Does that mean that if you do a -- if you clean out the colon, as you say, do you call the patient back in five years? Whereas, if you do CAD with optical, you -- and you see some residual small polyps that you don't call them -- you call them back in two years? I mean, are we talking about a difference in intervals here, which is a potential benefit for the cleaning out?

DR. WONG: No, what we do is if we find an adenomatous polyp and it's less than-- a single one less than say seven or eight millimeters, we call them back in five years. If we find three polyps that are six millimeters or greater, they come back in a year. And if we find a polyp that is greater than a centimeter, they come back in a year for another re-look.

DR. BERRY: So this is a much more complicated setting. Now, there is an

additional possible dimension to the benefit of -- or risk of CAD.

CHAIRMAN GLASSMAN: Okay. Are there any other comments? Yes?

DR. SPINDELL: Again, I would just like to make sure that we are talking about CAD colonography versus colonography, as what we are trying to evaluate here. Because it seems like we keep on getting into the colonography versus colonoscopy argument, which is not what, I don't -- which I believe is not the purpose of this issue.

CHAIRMAN GLASSMAN: You took --

DR. BERRY: But doesn't it lead to that?

CHAIRMAN GLASSMAN: -- the words right out of my mouth.

DR. SPINDELL: It does lead to that, but what we're trying to say here is colonography has a certain role. Does CAD improve the role of colonography or not? Not does CAD improve the colonoscopy colonography.

It does -- if the radiologist reads a colonography and get a result, and then they read it with CAD and they get -- what is the difference in those readings?

I think that's what the purpose is and not to determine whether it is colonography or colonoscopy.

CHAIRMAN GLASSMAN: You said it better than I was about to. Thank you. One more comment from Dr. D'Orsi, and then we're going to close this question.

DR. D'ORSI: I still have a little problem with the difference in the way you handle those two findings. If you -- if the CAD says I see three, four, five millimeter polyps and nothing else, you don't do anything about them. If the CAD says I see one seven millimeter polyp and three five millimeter polyps you would go, I assume, most of the time or some of the times to colonography and remove the five millimeter polyps. That's what I'm having trouble reconciling.

DR. KIM: They would go to colonoscopy not colonography.

DR. D'ORSI: I'm sorry, that's what I meant. You would go to colonoscopy and remove everything that you see. However, if the CT exam identifies only three or four five millimeter polyps, that person would not go on to colonoscopy.

DR. KIM: That is correct.

DR. D'ORSI: That's what I'm having a problem with.

DR. KIM: Right.

CHAIRMAN GLASSMAN: Okay. Well, if this is --

DR. SPINDELL: If we get into that discussion, the other thing we have to, you know, understand is they may not be then, but they're going to come, as we said before, back and get another one, and they may eventually have that colonoscopy. So you're just putting off the inevitable or not?

DR. D'ORSI: Suppose they don't

come back.

CHAIRMAN GLASSMAN: The last -- no. Dr. D'Orsi, hang in there. Last comment to the last question.

DR. KIM: So the question is if there is a seven millimeter and a bunch of diminutive lesions, we would send them to optical colonoscopy? If it's just several diminutive lesions, the person would go into normal screening which currently is five years at CTC, and that is correct.

And the reason why there is this dichotomy is because up to, or before CTC, the way that screening was performed with optical colonoscopy is the practice of universal polypectomy or clearing the colon.

And so, once they leave CTC and go to optical colonoscopy, it's going to that sort of strategy employed by the gastroenterologist. If it's just diminutive lesions, we do not report them. And the main reason why is because that the possibility of

the true target lesion being in that group, size group or the possibility of it being a tiny malignancy is so small that the risk probably -- the risks are not worth it to send the person to the risk of sedation. The risk of perforation although small, it's possible.

And in the risk/benefit sort of analysis, that is felt to be so small that we would just not report it. And that the few lesions, and remember, they are benign, they are not cancer, that are important, will continue to grow over time, and you should capture them at the five year interval which is the normal screening interval.

CHAIRMAN GLASSMAN: Okay. Thank you. Let me try to summarize the answer to question C1 for everybody. There is evidence of improved sensitivity to detect polyps using CAD over doing virtual colonoscopy without CAD. There is some evidence that there is a decrease in specificity that goes along with that.

And that somewhere between six and 10 millimeters, depending on whether you are a gastroenterologist or a radiologist, you come up with the critical size. CAD should be used as a second read; and therefore, there will be no reduced reading time evident with CAD added to virtual colonoscopy.

And that CAD itself doesn't guide optical colonoscopy. It's the virtual exam. It's late in the day. The virtual exam, not the CAD, that does that function. Does that answer question C1 adequately?

MS. BROGDON: Yes, thank you.

CHAIRMAN GLASSMAN: Yes. Thank you. Okay. Let's go on to two out of seven. Establishing ground truth, whether disease is present and if so, its location and extent is crucial for the evaluation of the performance of any CAD device. Please provide your recommendations for defining ground truth for colon CAD devices. And we have also touched on this a little bit.

Let me open this up for discussion. Ground truth for CAD, Dr. Dodd?

DR. DODD: I think this is a situation where colonoscopy, optical colonoscopy can provide the gold standard. I think you don't necessarily have to have a segment on blinding although it is recommended.

In the ACRIN trial, they did call back patients for whom something was seen on the CTC that wasn't seen on the colonoscopy. They did have patients who returned. This happened in a small number of patients, but in order to get around the problem of optical missing things, that is another strategy.

I would also like to say that you don't necessarily have to have all of the negatives undergo the optical if you are trying to be efficient in how you are planning your studies. So you would certainly send all positives on to get the optical and some proportion of negatives.

CHAIRMAN GLASSMAN: Other comments about the most effective? Because I mean, there were certainly some question about whether optical alone with the potential 11 percent miss rate actually represents ground truth.

DR. KIM: I think in terms of burden, optical colonoscopy with segmental unblinding would be somewhat difficult to do. And I would say that you probably could get a way for the positives to use optical colonoscopy and then for those discordant cases, CTC false negatives versus OC false -- sorry, CTC false positives versus OC false negative, which one is right.

I would say that you could either do a follow-up CTC, and if it's persistent, in our experience, all of those have been realized pretty hard for stool to hang around like that.

For the negatives, I know that in Wisconsin, that would be impossible for us to

send negative people on to optical colonoscopy. And I would say that maybe either like a consensus of experts to confirm that it truly is negative or maybe follow-up exams when we get it, could serve as the ground truth for that.

CHAIRMAN GLASSMAN: Any other comments about ground truth?

DR. SWERDLOW: I'll just --

CHAIRMAN GLASSMAN: I would like a few more comments, please.

DR. SWERDLOW: Well, where we are were, we have lots of gastroenterology fellows doing the optical colonoscopy. I think our complication rate and false negative rate is probably in excess of 11 percent. So we are trying to segmentally unblind everybody right now, but our numbers are still small.

But I agree, I think that's going to be very burdensome for industry to actually do. But they will probably have a different population of gastroenterologists to deal with

than we do.

DR. ROSENBERG: A question?

CHAIRMAN GLASSMAN: Yes.

DR. ROSENBERG: Negatives defined as no polyp over 10 millimeters, no polyp over six millimeters?

DR. KIM: No five millimeter.

CHAIRMAN GLASSMAN: No polyps five millimeters or less.

DR. LIN: I don't think that's completely decided yet for the negative of this. It's not clear, you know. So I think the segmental -- I would agree that segmental unblinding is very cumbersome although several of the largest CT colonography studies have used that as the gold standard. And it probably is the best assessment of the colon that we can have right now.

Other alternatives may be adequate, like for example, rescanning the colon after a while, following the patient, et cetera, et cetera. But if you're talking about a gold

standard, which I assume that's what you mean when you say ground truth, the segmental unblinding is really, I really think, the only option. And you know with the understanding that it is cumbersome.

CHAIRMAN GLASSMAN: Is it so cumbersome that it would fall outside of the, what's the term that you all used, least burdensome?

DR. LIN: It's hard to say. Dr. Wong has experience with that trial. Maybe he can comment on that.

DR. WONG: Well, you know, it's a difficult trial to do. But I mean, I think that's -- if you want to compare and see whether a polyp really exists there, that segmental unblinding would be the best way to look at that.

And actually, when you use gold standard, the ultimate truth is really a combination of CTC plus optical colonoscopy. If you really want to know whether you've got

a polyp in your colon or whether you are missing something, they are actually complementary studies.

The difficulty with colonoscopy is that you can't see backwards. You can see forward, but you can't retroflex and come all the way back in the retroflex position; whereas, CT colonography can see behind folds. So it actually is a complementary study.

Again, you know if you really wanted to do a perfect study, there's a study that we did originally, and that's to segmentally unblind. It really holds everybody to the fire because you know specifically whether you make a mistake or not. And even then, occasionally you will miss something because things hide behind folds.

CHAIRMAN GLASSMAN: Right, but here we are sitting at the FDA Panel knowing that for devices sometimes the perfect test is not the one that is able to be done. And the

advice that the Agency needs from us is for ground truth for evaluating CAD. What is good enough? And I'm not sensing that I'm getting an answer yet.

DR. KIM: I would say what is good enough for the positives is the optical colonoscopy. And really, the -- what you are talking about for ground truth for the CTC false positive, that is you see a polyp that optical colonoscopy did not confirm, that really is a very small percentage of cases.

Our experience in over 5,000 patients our OC correlation rate is over 90 percent. So, one in 10 of those and most of those are for actually small ones. But actually, it really is a small portion that we are talking about. And I would say in that subgroup, that it would be acceptable to have either a panel or bring the person back for a second CTC.

CHAIRMAN GLASSMAN: Is there anyone who is opposed to that scheme? No?

DR. GARRA: What's the scheme again?

CHAIRMAN GLASSMAN: The scheme is optical colonoscopy for the positive studies and for the follow-up: CTC or expert panel for the --

DR. GARRA: Discordant cases.

CHAIRMAN GLASSMAN: -- discordant cases. Okay. That all right for everybody? Brian?

DR. GARRA: What about negative cases?

CHAIRMAN GLASSMAN: Okay, what about negative cases? One year follow-up CTC or optical. I mean, what would be -- if we make it 5 year follow-up, the industry will never get --

DR. GARRA: No.

CHAIRMAN GLASSMAN: -- a study.

DR. GARRA: We should just do both studies.

DR. KIM: Currently, CTC is a

clinical program. There is no way we could ever get patients to come back in a year if we told them it was negative. So I would say that if it's a negative exam, that maybe a panel, I don't know.

DR. GARRA: How about if you told them it's negative, but you might have missed something? Then they would probably come back. Having had several polyps removed from my own colon.

CHAIRMAN GLASSMAN: What about, I mean, an expert panel looking at the negative? Is that a reasonable safeguard in terms of evaluating CAD? Is it? Does anyone --

DR. GARRA: I think so since we are not evaluating CT colonoscopy.

CHAIRMAN GLASSMAN: Right, right. We are evaluating CAD.

DR. GARRA: Yes.

CHAIRMAN GLASSMAN: Is there anyone who is opposed to that as the evaluation for the negatives? Okay. Ms. Brogdon, in regards

to C2, the panel feels that for evaluation of CAD, that an optical colonoscopy for positive cases and follow-up virtual colonoscopy for discordant cases; and an expert panel for negative cases is adequate for determining ground truth. Is that acceptable or is that enough information for you?

MS. BROGDON: That's clear. Thank you.

CHAIRMAN GLASSMAN: Okay. She said clear. I don't know. She didn't say acceptable, but that's fine. Okay.

DR. GARRA: We could always have a few anchor points and throw in a few --

CHAIRMAN GLASSMAN: Well, let's move on.

DR. GARRA: -- dual cases or people --

CHAIRMAN GLASSMAN: Okay. Yes.

DR. GARRA: -- done twice, because that -- people will go for that. Patients will accept that.

CHAIRMAN GLASSMAN: I think we have got an answer for that one.

Let's go on to C3, please. Please discuss the role of standalone performance testing in clinical evaluation of colon CAD devices.

(a) If you believe standalone testing should be requested in the evaluation of these devices, please provide your recommendations and comments on whether certain substrata, nodule size, say pathology, co-morbidity, CT dose, imaging protocol, et cetera, should be considered in device testing and labeling.

(b) If you believe that there are specific situations where standalone performance testing may not be important, please, comment on what those might be.

Don't be shy. Dr. Swerdlow?

DR. SWERDLOW: Okay. I think here some things are fairly analogous to this morning. I think because we had the similar higher prevalence of things, we don't

necessarily need to mess with the datasets as much as we might for mammography.

And ultimately, I think, the key number -- the key thing that we are all wrestling with is size and trying to get a handle on that. So I think that's probably absolutely the number one thing that a CAD system would be able to show, that it functions at the 10 millimeter level, at such a sensitivity and perhaps at the six millimeter level at such another sensitivity.

And as far as Part B goes, I think, standalone performance is important, just like this morning.

CHAIRMAN GLASSMAN: Yes, Dr. Wong?

DR. WONG: Yes, again, I think what you really need is to have a large repository, make sure that the cases are proven cases of lesions that have been found, you know, in previous CTs; and that this repository ought to be really kind of well-guarded so that whenever the device makers come in with their

particular device, there is no pre-learning of the type of cases that you have.

CHAIRMAN GLASSMAN: Other? We need more input. Yes?

DR. KIM: For standalone testing, I think it will be really important as Ron Summers pointed out that the conditions in which the testing is done is known, and that if the CAD is being applied to say tag cases for stool and fluid tagging. What is the slice collimation of the scanner?

I think most people agree that 2.5 is probably the upper limit, 2.5 millimeter. 1.25 is certainly acceptable. And when you get below seven millimeter imaging, you really don't gain that much and then dose.

So you want to make sure that, you know, we have really pulled down the dose and with two current modulation to make sure that the CAD is working effectively at these doses.

CHAIRMAN GLASSMAN: Other comments?

DR. LIN: No, I would agree with

all that that has been said.

CHAIRMAN GLASSMAN: Anyone else, any comments about question C3? Okay. Let me try to summarize C3. We believe that standalone testing should be requested in the evaluation of these devices. That the conditions of the underlying CT need to be known at the time of the standalone testing because it will affect the sensitivity and the clinical relevance of the imaging.

Nobody -- in fact, let me stop for a second, because we really didn't answer the issue of substrata and I think we need to. That's -- we missed that: nodule size, shape, pathology, co-morbidities. I mean, we talked about CT dose and imaging protocol.

But what about for the standalone? Should there be varying size polyps? I mean, I don't --

DR. KIM: Yes, I think size is the main thing here. All of the other descriptors really do not correlate well in terms of

representing the precursor target that we are looking for, and size is the one thing that we can look at from a CAD perspective, from CTC perspective that does correlate well knowing that large size, there can be more of the true target lesions in this group.

CHAIRMAN GLASSMAN: What sizes should we include in this? Six millimeters and above?

DR. KIM: I think that's reasonable.

CHAIRMAN GLASSMAN: Okay, so to come back to my summary here. Standalone testing should be requested. Polyps six millimeters in size or greater should be included. The CT protocol and imaging protocol and CT dose is important to know that the images were obtained at clinically relevant situations, so that CAD will then be a valuable -- evaluatable in a clinically relevant way.

And that we think that standalone

testing is important, and therefore, we did not come up with any times when we wouldn't do it. Does that reflect our opinion, Dr. D'Orsi?

DR. D'ORSI: Can I just get an opinion on location, if that's helpful to you? Should that be in standalone testing or is that not helpful if you're going to go to optical colonography?

DR. KIM: I guess I'm not quite certain in terms of the ability to detect a polyp in a given location. Is that the --

DR. D'ORSI: Yes. In other words, if you have two or three separated by maybe eight or 10 centimeters, does it help you to know fairly precisely, not exactly, where they might be so you spend extra attention looking for that or is that useless?

DR. KIM: Usually, you know there are discrete polyps, and so it's not an issue of being in the general area. You know you see a polyp in the sigmoid, or you see a polyp

in the rectum, or you see a polyp in the cecum. I guess I'm not understanding.

CHAIRMAN GLASSMAN: I think we are confusing maybe CAD with colonography here. We need to be careful we're talking about CAD. Dr. Rosenberg?

DR. ROSENBERG: In reference to co-morbidities, are there any that would affect CAD, diverticular disease, or any other common problems that should be included or excluded?

DR. KIM: I think diverticular disease probably would affect CAD as well as CT colonography. Often the sigmoid is involved, and you get this sort of mycosis or mild diffuse thickening where you can never really distend the sigmoid. So I think CAD would not perform as well there. So perhaps that would be one area.

CHAIRMAN GLASSMAN: What about the others? Dr. Wong?

DR. WONG: I think it's also reasonable, because you want the CAD to be as

good as your virtual colonoscopy. At least you want to have it identify those lesions. So geographically, you know there are difficult -- just like colonoscopy. I'm sure that the flexures, different areas where the colon bends, that it's more difficult to identify polyps in those areas so certainly those difficult cases ought to be added into this test bracket.

DR. ROSENBERG: So that location would be a --

DR. WONG: I think location would be important, yes.

CHAIRMAN GLASSMAN: What about the co-morbidity of diverticulosis?

DR. KIM: I would think so.

DR. WONG: I would agree.

DR. LIN: That might possibly be a factor affecting the accuracy of colonography and perhaps CAD as well, in addition to that. So I mean, I think what they are trying to get at here is it's almost like stress

testing. I mean these are potential situations where the accuracy of colonography is going to be affected whether it is because of a polyp located in a certain area of the colon that's traditionally difficult for virtual colonoscopy or whether it is polyps of a certain shape like very flat polyps.

So maybe that's what they are getting at and --

CHAIRMAN GLASSMAN: Well, I think what they want is what we are getting at, rather than what they are getting at. So what I have got since we've started the summary here is, in addition, polyps in different locations and at least one co-morbidity of diverticulosis.

And, you know, what about polyps of different shapes? Flat polyps, pedunculated polyps?

DR. KIM: You know, I would say that flat polyps are the one -- you know, are going to be the polyp that would be more

difficult for CAD and for CT colonography. Again, if you are looking at sphericity or how rounded a lesion is for your CAD to find that, and so you know, certainly, I think that a flat polyp would be harder to see. And perhaps we should try to stratify that.

One thing, before I forget, is with the standalone testing, I think, it's also important to kind of get the demographic populations of their training set characteristics so that you know that you are sort of comparing equivalent -- so if you see a performance that your -- between different CAD systems that you can sort of see how they are doing across, if the results truly translate or not.

Because I think if the training sets are markedly different, a CAD may look like it's doing better, but when you apply to a low prevalence situation, it may not be the case.

CHAIRMAN GLASSMAN: So we seem to

be talking now about certainly an enriched dataset and possibly a stress dataset for our statisticians. Is that any -- are there unique problems here that we need to be aware of that are different from the ones we discussed this morning or are they the same?

DR. DODD: I think they are the same. So I think we have to be careful with generalizing. Again though, here we are talking about standalone testing where I think we want to categorize the performance with specific categories.

So I'm okay with that. When we move to reader studies, we want to talk about the average reader performance, and that's where stress testing to me seems not as desirable.

CHAIRMAN GLASSMAN: Okay. Let me try the third time for the answer to this one, the summary. Let's see if I can do any better.

Okay. Standalone testing is

important. Polyp size, minimum six millimeters and larger. The CT dose and imaging protocol needs to be known to make sure that it's clinically relevant. We want to enhance the set with polyps of varying locations, including the flexures which may be more difficult to find.

We want to enhance with flat polyps that we know are more difficult to find. And we want to know the demographics of the test set to make sure that it is clinically appropriate with the usual patient population. And that we believe that standalone testing is important in all instances.

Do I have it right? Dr. Rosenberg? One more time.

DR. ROSENBERG: I'm sorry. Co-morbidities, diverticular?

CHAIRMAN GLASSMAN: Thank you, diverticulosis. I got lost in my own handwriting. And patients with diverticulosis. Ms. Brogdon, is that an

adequate response to the question?

MS. BROGDON: Yes, thank you.

CHAIRMAN GLASSMAN: Thank you. Okay. C4. Please discuss the role of reader performance testing in the clinical evaluation of colon CAD devices.

(a) Do you think it should be considered in the evaluation and, therefore:

(i) What are the appropriate primary endpoints in corresponding clinically significant effect sizes? Comment on ROC analyses;

(ii) The merits of per lesion, per segment and/or per patient endpoints in the assessment of endpoints;

(iii) And whether reading time should be assessed, and if it, how?

(b) If you believe that there are specific situations where reader performance testing may not be necessary, please comment on what those might be.

Who would like to begin the

discussion on reader testing, given what we have said about standalone? Dr. Lin, any ideas?

DR. LIN: I think that's similar to the situation with mammography CAD, any improvement in the sensitivity or specificity. And I think I talked a little bit about my opinions on ROC curve analysis. You know, I use it all the time usually in situations like alpha fetoprotein you know, in trying to determine cut-off level.

And I think this is a little bit different. Even though we're able to score, we're able to come up with a score, but as I said, essentially the decision is really whether or not to refer the patient for colonoscopy. There is really -- it's really sort of a binary kind of -- I mean, there may be a third option where we put them into some sort of surveillance program with CT colonography.

But there aren't that many points.

There aren't going to be that many points on ROC curve. You know if you look at the C-RADS rating scale, most of these categories will lead to colonoscopy. There is only a few where there might be some question. So that's my thought on the ROC curve question.

We talked a little bit about stratification by polyp size, shape and location. And that seems to be a good idea.

And with regard to reading time, just like with mammography CAD, that should be assessed as well.

CHAIRMAN GLASSMAN: What about per lesion, per segment, and/or per patient?

DR. LIN: Well, I think the most important endpoint is going to be per patient because that determines what you do with the patient. You know you're going to -- if you find one polyp, you're going to send them -- one large polyp, you're going to send them for a colonoscopy. If you find two polyps, two large polyps, you're still going to send them

for colonoscopy.

The other endpoints by polyp, by lesion, et cetera, et cetera, might be helpful in terms of guiding the optical colonoscopy.

CHAIRMAN GLASSMAN: Let me ask you a question about that because if we were -- I would agree with you about per patient, if we were evaluating virtual colonoscopy as a test.

But when we are evaluating a technique that is supposed to simply find lesions, isn't necessarily per lesion analysis actually more important for evaluating CAD, as opposed to evaluating optical colonoscopy versus virtual colonoscopy?

DR. LIN: I think that's a good point. I think I might have to agree with that in that particular situation, you know.

CHAIRMAN GLASSMAN: Other comments, please, about C4? Okay.

DR. LEITCH: I think it's still again in screening a mass population, the question of if CAD improves the sensitivity of

screening in that population so that's why I think the per patient thing makes sense when you are -- you know, when you start talking about the application of a screening tool and a large population.

That's why the time thing starts to -- you know, that's -- I mean, to me, this is a circumstance. We're trying to get a technique to, you know, replace the reader. You know it's kind of the goal of this one, in a sense. But I think these time factors have to be, you know, taken into consideration. And how you can impact the overall process of screening for the population?

CHAIRMAN GLASSMAN: Dr. Swerdlow?

DR. SWERDLOW: I think the time factor is certainly very important, but it doesn't necessarily -- it's certainly not going to affect a particular CAD system sensitivity. And ultimately, when somebody is trying to decide whether to buy one or not or to choose between two different systems, if

you have two that function equally well and one is slow and cumbersome and one is faster and easier to use; the market forces are going to determine which one to use.

And I think, you know, the manufacturer is going to take that into consideration as they design the product. I don't know that it is such a key for the industry to present their data in terms of time. It's more useful as an academic pursuit to us.

CHAIRMAN GLASSMAN: What about per lesion, per patient, per segment?

DR. SWERDLOW: I don't really see how per segment fits in very well. I tend to agree, I think, per patient is the endpoint because you very quickly move from, you know, there's nothing to colonoscopy, optical colonoscopy. The question then falls back to threshold. Is the threshold 10 millimeters or six millimeters?

If it's a six millimeter, we're

only going to find one or two polyps that we're going to follow. Well, then we need to start talking about lesion sensitivity clearly.

CHAIRMAN GLASSMAN: And ROC curves, any opinion?

DR. SWERDLOW: Nothing to add there.

CHAIRMAN GLASSMAN: Okay, Dr. Garra?

DR. GARRA: Of course, I have something to add there. I don't think the C-RADS scale would necessarily be appropriate for ROC analysis. I can't read the slide that well so it's shrunk down a little too much. But the simple way to do that would be to just rate your confidence like on a 100 point scale.

Are you sure this is a polyp or not? And then we could have the person record their size and that would be -- give you all the information you need to generate a robust

ROC curve assuming that the people were trained to know that they need to use the entire scale, not a portion of the scale.

The other thing was, though, per lesion versus the entire colon. It doesn't really cost you anything to gather that extra information. You know, have them record the location and the segment, and you have that information to help you analyze what's going on if your performance is not what you expect it to be.

So I would say by all means do do per lesion, per segment as well because you can gather that for free almost.

CHAIRMAN GLASSMAN: But in terms of the study design for endpoints, you think per patient, if I'm quoting you correctly?

DR. GARRA: I'm sort of on the fence. I think I'm tending a little bit to be a little bit more like you that I would prefer per segment or per lesion, but -- rather than per patient.

CHAIRMAN GLASSMAN: Okay.

DR. TOURASSI: Well, I would echo that. When you do a reader observer study, you ask them to mark every lesion, every polyp, every segment, this is a time consuming study. It's very different than saying per patient. What are you going to do if I tell you -- if I mark certain polyps?

So for the observer study, to keep it feasible and to be able to collect the data, I think we need to look at is this tool going to change patient management? And patient management is what are you going to do with this patient now that CAD has marked for you so many polyps?

Does it really make any difference if the system marks three versus five versus 10 of the little small ones if, in the end, patient management remains the same?

DR. GARRA: That's an interesting question. I think when you want to evaluate the system, that's what you have to do. You

have to determine if it's marking 20 lesions, that's probably too many. And you -- but you have to determine your confidence on the lesions that are marked.

And it is time-consuming and you wouldn't want to do it in regular clinical practice, but this wouldn't be clinical practice. It would be a clinical trial so I would do it.

DR. TOURASSI: But the per lesion analysis will still be part of the standalone performance. We're talking about the reader observer study.

DR. GARRA: Yes. Well, I think we are talking -- yes, if we're going to do an observer study, then I think the observer needs to give their confidence level for their lesion since they are identifying the lesion anyway. I don't quite understand how this is going to change anything, unless you want them just to say yes, it's abnormal or no, it's not abnormal.

That would be simplifying, but it wouldn't give you that much information. If something wasn't working properly, it wouldn't tell you anything about what was going wrong.

DR. TOURASSI: I'm confused now.

CHAIRMAN GLASSMAN: You're not alone.

DR. GARRA: Maybe I wasn't answering the right question, but I don't -- I didn't foresee that people are going to have 20 or 30 lesions that they are going to be uncertain about in one of these typical studies. So that's part of the question I didn't understand.

I don't think it would be that burdensome for somebody who knows they are undertaking a study to evaluate the performance of a CAD product to actually look at all the marks and determine what they are.

CHAIRMAN GLASSMAN: Again, remember we are talking about a product who is -- whose endpoint is the detection of a polyp, not

optical colonoscopy. And so I'm a little bit concerned obviously about the per patient, but you know it's a group decision.

And by the way, this -- we're going to quit for the day after this question. We're losing some panel members, and so I think we will pick up tomorrow morning with C5 after the Closed Session. We are reasonably close to being done, I hope.

But let's continue on with this discussion, because this is a very important question that we need to deal with.

DR. GARRA: Yes, I think if you are doing an observer study and you are looking at lesions, it's not overall outcome that you are interested in so much as the performance of the actual CAD system. And I think then, that's what you need to do. You need to look at what it's marking.

And people are going to be doing that anyway so they are just going to be not saying anything about the ones that they think

are below their level of threshold.

DR. TOURASSI: But we're talking about the study that will compare the performance of radiologists without and with the CAD system. So I still can't see what's the value of having a radiologist agree with the CAD, that indeed, there are three or five, whatever, small lesions if in the end, the system, the device is not going to make any difference in terms of clinical outcome for the patient, patient management.

DR. GARRA: Well, I'm not sure in the cases where the radiologist agrees. It's not a matter of agreeing or disagreeing. He is taking -- the radiologist is taking the information and deciding whether they think there is a polyp really there or not, okay?

And the CAD system is marking things that might be. So I think the radiologist is still responsible for making that decision. And isn't that what they would do in a real clinical practice anyway, look at

each of those and decide?

So in this case, we are just simply asking them to record that instead of just mentally taking note and not reporting the ones that they don't think are important.

DR. LIN: I think in clinical practice, the radiologist doesn't give a score as to how confident they are that there is a polyp there. So in order to do the ROC analysis, it sounds like they will have to come up with that kind of score. And it's not clear to me what kind of advantage between the ROC analysis.

DR. GARRA: That's the fundamentals of ROC analysis is that you have to do a reading which most people don't. They do a binary decision. But that's the difference between doing an ROC study and doing a sensitivity/specificity study. Is that, you know, in a sensitivity/specificity, you have an unknown decision threshold, and you're making a binary decision.

In an ROC study you are forced to space them out on a plot, and that allows you to get that extra information about where your decision threshold is.

DR. LIN: Okay.

CHAIRMAN GLASSMAN: Any other comments? Yes?

DR. SPINDELL: So again, like many of you, I'm still a little confused because I don't know if the purpose of CAD is to detect lesions. Why wouldn't it be a per lesion study? And I understand that one patient may have three or four, but in the study, in the clinical study to prove efficacy, you're really looking at polyp types.

And some patient may have five polyps. One polyp may be a very difficult polyp to see for radiologists that CAD should or hopefully will pick up. And all that you are basing it on is that they found a regular two centimeter polyp and missed this very difficult six centimeter polyp. You're not

going to get an understanding for how -- what the clinical benefit of CAD is and what the true benefit is just because that one patient, who happened to have the hard one, also had a real easy one.

CHAIRMAN GLASSMAN: Dr. Wong?

DR. WONG: I think that, you know, when we are trying to evaluate the CAD system, I think it would be very important that we try to get as much information as we can. So I think not -- just getting the large sized polyp and saying well, ultimately, that is what we're going to do clinically. I think we are really missing the point here.

I think we need to get per polyp, per lesion. It gives us a real good idea of how good this CAD system is. So I personally would feel that at this stage, as we begin to look and regulate what we're going to be looking at, we need that information.

CHAIRMAN GLASSMAN: Is there a general -- okay.

DR. CARRINO: I was just going to say I think the analysis should be per lesion and inherent to that is the location or the segment. So I would just reinforce that.

CHAIRMAN GLASSMAN: Dr. D'Orsi?

DR. D'ORSI: Yes, I think -- first of all, I don't think the clinical workup of the patient is the same from what I have heard. If you have -- for example, if you don't do per lesion, then you -- somebody sees three or four five millimeters polyps and there is one three millimeter -- three centimeter polyp hidden in a flexure that is not seen, that patient will not go to colonoscopy.

So there is a possibility that you are going to not see something and not deal with it the same way. If somebody said to me every polyp I see I'm doing a colonoscopy and I'm going to take them out, then I would agree with that. But it doesn't seem to be that way from what I'm hearing. So I think a per

lesion, even with the observer, is important.

CHAIRMAN GLASSMAN: Dr. D'Orsi?

DR. D'ORSI: I think I would agree with that. I think per lesion, we've had this discussion, is probably --

DR. LIN: So I think --

DR. SAHINER: If you are talking about per lesion and by location, then I think we are talking about FROC and not ROC. Am I correct?

CHAIRMAN GLASSMAN: I need help here.

DR. GARRA: I can -- let me address that.

DR. SAHINER: Craig raised --

CHAIRMAN GLASSMAN: Let's let Dr. Dodd, first.

DR. SAHINER: Oh, sorry.

DR. DODD: Yes, the answer is yes.

DR. GARRA: However, you can take the -- if you do it per lesion, you can convert that into true ROC, because you'll

also know the segment and then you can go per segment and then you are into zones. So you can convert it fairly readily.

DR. DODD: When you are looking at per segment. Not when you are looking at per lesion.

DR. GARRA: Right. You lose precision on your location, but you gain in having a more attractable ROC curve.

CHAIRMAN GLASSMAN: Are -- have we come to a consensus here? I'm seeing nodding. Let me try unofficially to come up with a statement, and you all can respond to it. I'm not going to make the same mistake I did with the last question and leap right into the final and go through it four times.

Okay, we believe that reader performance testing should be done. Clinically effective sizes are six millimeters and greater. ROC analysis is appropriate, as is FROC analysis, but either one. And that the general consensus was that the endpoint

should be per lesion, rather than per segment and per patient, knowing however, that if we choose the ROC analysis, it would be converted to a per segment analysis.

And reading time should be assessed. And now, the last part, do we believe there are situations? Again, we may be talking about algorithm changes or something where performance testing, reader performance testing may not be necessary.

Part B, what do we think? The last thing for the afternoon, what do we think about that? Minor changes in algorithm, that standalone testing would be adequate, but for major changes -- similar to what we thought about this morning.

DR. GARRA: Yes.

DR. WONG: Yes.

CHAIRMAN GLASSMAN: Okay.

DR. CARRINO: Similar to this morning, but we still have to decide what minor would be.

CHAIRMAN GLASSMAN: Yes, that's what the FDA is going to do for us, I hope.

MS. BROGDON, I hope you were taking notes.

MS. BROGDON: I was. I would just like for you to say for the record that you believe your recommendations on Part A are least burdensome.

CHAIRMAN GLASSMAN: If I say it, will anybody disagree with me? We think it's least burdensome. Is that -- yes? Is that adequate for this question?

MS. BROGDON: Thank you.

CHAIRMAN GLASSMAN: Ah, thank you all very much for hanging around. I know we went over, and we will pick up tomorrow morning. We have a closed session at 8:00 that is supposed to end at 8:30, and we will pick up with C5 in the morning and try to stay on track better tomorrow.

I apologize to those of you who are going to miss your dinners. Thank you.

(Whereupon, the meeting was concluded at 5:58 p.m.)