UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

RADIOLOGICAL DEVICES PANEL

+ + + + +

OPEN SESSION

WEDNESDAY, MARCH 5, 2008

The Panel met at 8:30 a.m. in the Grand Ballroom of the Hilton Washington DC North, 620 Perry Parkway, Gaithersburg, MD, Leonard M. Glassman, MD, Acting Chairman, presiding.

PRESENT:

LEONARD M. GLASSMAN, MD Acting Chairman
NANCY WERSTO Executive Secretary
JOHN D. BOURLAND, PhD Member
CARL J. D'ORSI, MD Member
BHARAT B. MITTAL, MD Member
MARVIN C. ZISKIN, MD Member
CRAIG K. ABBEY, PhD Temporary Voting Member
DONALD A. BERRY, PhD Temporary Voting Member
JOHN A. CARRINO, MD Temporary Voting Member
LORI E. DODD, PhD Temporary Voting Member
BRIAN S. GARRA, MD Temporary Voting Member
DAVID KIM, MD Temporary Voting Member
MARILYN LEITCH, MD Temporary Voting Member
OTTO LIN, MD Temporary Voting Member
ROBERT ROSENBERG,MD Temporary Voting Member
BERKMAN SAHINER,PhD Temporary Voting Member
KENNETH J. STEIER, DO, MPH, MHA Temporary Voting Member

PRESENT: (continued)

DANIEL SWERDLOW,MD	Temporary Voting Member
GEORGIA D. TOURASSI, MD	Temporary Voting Member
A. CHRISTINE WATT, MB, CHB	Temporary Voting Member
ROY K.H. WONG, MD	Temporary Voting Member
NANCY FINKEN, MFA	Consumer Representative
DAVID SPINDELL, MD	Industry Representative
NANCY BROGDON	FDA

TABLE OF CONTENTS

P R O C E E D I N G S

Time: 8:30 a.m.

CHAIRMAN GLASSMAN: I would like to call this meeting of the Radiological Devices Panel to order.

I am Dr. Leonard Glassman, Chairperson of the Panel. I am a diagnostic radiologist in private practice in the Washington, D.C. area. I am also the American College of Radiology Breast Imaging Scientist at the Armed Forces Institute of Pathology, and I am Clinical Professor of Radiology at George Washington and at Georgetown, and I am an expert in diagnostic ultrasound and in breast imaging.

If you haven't already done so, please sign the attendance sheets outside on the table by the doors. The agenda for this meeting is also available outside the door.

If you are presenting in any Open Public Hearing session today and have not previously provided an available electronic copy of your presentation to the FDA, please arrange to do so with Sunder Rajan. Sunder, can you raise your hand so everybody knows where you are?

Okay.

If you could please silence all your cellphones, that would be appreciated.

I would like to announce the remaining tentatively scheduled meetings of this Panel for 2008: August 12 and November 4th. Please remember that these are tentative dates. You may monitor the Panel website for updated information.

I note for the record that the voting members present constitute a quorum, as required by 21 CFR, Part 14.

Ms. Wersto, our Executive Secretary for the Radiological Devices Panel, will make some introductory remarks.

MS. WERSTO: Good morning, everyone. Before I turn the meeting over to Dr. Glassman, I am required to read the Conflict of Interest statement into the record.

FDA Conflict of Interest Disclosure Statement, Particular Matters of Applicability: Radiological Devices Panel of the Medical Devices Advisory Committee, March 4-5, 2008.

The Food and Drug Administration is

convening today's meeting of the Radiological Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the Industry Representative, all members and consultants of the Panel are Special Government Employees or Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to Special Government Employees who have financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to Special Government Employees and regular government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussions of today's meeting, members and consultants of this Panel who are Special Government Employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

The agenda involves a general discussion of computer aided detection and diagnosis (CAD) devices for radiological images such as mammograms, chest X-rays and computed tomography of the lungs or colon.

The general discussion will focus on the

general methodologies for CAD, including how CAD devices are used in clinical decision making, how the devices are tested, and the information needed to properly assess their safety and effectiveness.

The general discussion will be followed by specific discussions related to mammography CAD devices -- that was yesterday -- colon CAD devices yesterday also, continuing today, and lung CAD devices. These discussions will include how the different types of CAD devices are used and the literature published regarding these devices with focus on testing issues related to the different devices.

This is a particular matters meeting during which general issues will be discussed.

Based on the agenda and all financial interests reported by the Panel members and consultants, conflict of interest waivers have been issued in accordance with 18 USC Section 208(b)(3) and Section 712 of the Food, Drug and Cosmetic Act to Dr. John Carrino.

Dr. Carrino's waivers address personal consulting arrangements with a firm at issue. He receives an annual fee of less than $10,001 for these

arrangements, which are unrelated to today's agenda. The waivers allow Dr. Carrino to participate fully in today's deliberations.

FDA's reasons for issuing the waivers are described in the waiver documents which are posted on FDA's website at www.fda.gov/ohrms/dockets/default.htm. Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Office, Room 6-30 of the Parklawn Building.

David Spindell, MD, is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Abbott Laboratories, Medical Products Group. We would like to remind members and consultants that, if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue. Thank you.

Now for a few general announcements. Transcripts of today's meeting will be available for Neal Gross & Co. by calling area code 202-234-4433.

Information on purchasing videos of today's meeting can be found on the table outside of the meeting room.

Presenters to the Panel who have not already done so should provide FDA with a hard copy and an electronic copy of their remarks.

I would like to remind everyone that members of the public and the press are not permitted around the Panel area beyond the speaker's podium. The press contact for today's meeting is Peper Long. I don't know if she is here.

I request that reporters wait to speak to FDA officials until after the Panel meeting. Thank you.

CHAIRMAN GLASSMAN: Thank you, Ms. Wersto. Good morning, everyone.

At this meeting, the Panel will be making recommendations to the Food and Drug Administration on general issues pertaining to computer aided detection devices and on specific issues pertaining to mammography

CADs, colon CADs, and lung CADs.

Let me just say briefly to those of you who came back today to complete the colon CAD discussion, I apologize that we didn't finish yesterday, but we wanted to have a full discussion, and so I hope you will bear with us with that inconvenience to you.

Before beginning this meeting, I would like to ask our distinguished Panel members who have generously given their time to help the FDA in this matter being discussed today, and other FDA staff seated at the table to introduce yourselves.

Please state your name, your area of expertise, your position, your institution, your status on the Panel as voting member, deputized voting member, Consumer Representative or Industry Representative. Why don't we start with you, Dr. Spindell, on my right, and we will just go all the way around the table to Ms. Brogdon.

DR. SPINDELL: My name is David Spindell. I am the Vice President of Medical Affairs for Abbott Laboratories.

DR. KIM: I am David Kim. I am an Assistant

Professor of Radiology at the University of Wisconsin. My area of research is CT colonography, and I am a Temporary Voting member.

DR. LEITCH: I am Marilyn Leitch. I am a surgical oncologist at UT Southwestern Medical Center in Dallas. My special interest is in breast disease and also in screening for cancer, and I am a Temporary Voting Member.

DR. SAHINER: My name is Berkman Sahiner. I am an Associate Professor of Radiology at the University of Michigan. I am a Temporary Voting Member, and my interests are medical imaging in general and CAD in particular.

DR. CARRINO: I am John Carrino. I am Associate Professor of Radiology and Orthopedic Surgery at the Johns Hopkins University. My expertise is in picture archive and communication systems, and I am a Temporary Voting Member.

DR. ROSENBERG: I am Robert Rosenberg. I am a Professor of Radiology at University of New Mexico Health Sciences Center. My expertise is in mammography. Research interests are in breast cancer screening and

community outcomes, and I am a Temporary Voting Member.

DR. DODD: I am Lori Dodd. I am a mathematical statistician at the Biometric Research Branch at the National Cancer Institute. I have an interest in clinical trials in imaging, and I am a Temporary Voting Member.

DR. D'ORSI: I am Carl D'Orsi. I am Professor of Radiology and Hematology and Oncology at Emory University. My expertise is breast imaging, and I am a Voting Member.

DR. LIN: My name is Otto Lin. I am a gastroenterologist at Virginia Mason Medical Center in Seattle and also Clinical Associate Professor of Medicine at the University of Washington School of Medicine. My area of research interest is colon cancer screening. I am also a Temporary Voting Member.

DR. BOURLAND: I am Dan Bourland. I am a Radiation Physicist. I am at Wake Forest University, Department of Radiation Oncology and Biomedical Engineering. My interests are digital imaging and their uses in radiation treatment. I am a Voting Member of the committee.

DR. STEIER: I am Ken Steier. I am a Clinical Professor of Medicine, Division of Pulmonary and Critical Care at the Nassau University Medical Center in New York. My area of interest is interventional pulmonary medicine, and I am a Temporary Voting Member.

CHAIRMAN GLASSMAN: I have already introduced myself, Leonard Glassman. I have given you my affiliations, and I am a Voting Member.

DR. MITTAL: I am Bharat Mittal. I am Professor and Chairman of Radiation Oncology at Northwestern University. My area of expertise includes radiation oncology.

DR. ZISKIN: Marvin Ziskin. I am a Professor of Radiology and Medical Physics at Temple University in Philadelphia, and I am the Director of the Center for Biomedical Physics. My area of expertise is in safety and physics of ultrasound and electromagnetic fields, and I am a Voting Member of this Panel.

DR. WONG: My name is Dr. Roy Wong. I'm the Chief of Gastroenterology at Walter Reed Army Medical Center and Professor of Medicine, Uniformed Services University of the Health Sciences. My major interest is

in the esophagus and colon, specifically colonoscopy and CTC, and I am a Temporary Voting Member.

DR. ABBEY: I'm Craig Abbey. I am a researcher at UC Santa Barbara. I am an Adjunct Professor at UC Davis. My area of research is modeling reader performance, and I am a Temporary Voting Member.

DR. GARRA: I am Brian Garra. I am professor of radiology at the University of Vermont. I am Vice Chairman of Research and Director of Ultrasound. I am a body imager, and I am a Temporary Member of this Panel.

DR. WATT: I'm Christine Watt. I am a breast imager and Director of two breast centers and work for three separate hospital systems in the Detroit area. My area of expertise is mammography and breast imaging, and I am a Temporary Voting member.

DR. SWERDLOW: I am Dan Swerdlow. I am an Assistant Professor of Radiology at Georgetown University, Division of Abdominal Imaging. I am a Temporary Voting Member. My interests are imaging and biopsy of GI malignancies, including CTC.

DR. BERRY: I am Donald Berry,

Biostatistician, Chair of Biostatistics at M.D. Anderson Cancer Center and Head of the Division of Quantitative Sciences, and I am a deputized Voting Member.

DR. TOURASSI: I am Georgia Tourassi, Associate Professor of Radiology and Medical Physics at Duke University Medical Center. I am a Temporary Voting Member of this panel, and my area of expertise is CAD.

MS. FINKEN: My name is Nancy Finken. I am the Consumer Advocate on this Panel, a nonvoting member, and a retired educator here in the Washington area.

MS. BROGDON: I am Nancy Brogdon. I am not a member of the Panel. I am the Director of FDA's Division of Reproductive, Abdominal and Radiological Devices.

CHAIRMAN GLASSMAN: Thank you, everyone. I hope everyone has an agenda. We were a little bit short yesterday. The crowd was a little bigger, I think, than we expected. Now that you all have an agenda, we are not going to follow it completely. So be flexible, please.

We didn't finish yesterday with colon CAD. It was a very good discussion, sort of free wheeling, and we have a few questions to deal with.

Also, as a break with what we usually do, when we get to Question C7, part A -- How are colon CADs used clinically? -- the Chair will recognize any speakers in the audience for five minutes who want to speak particularly on that topic.

I know you are not prepared. You, unlikely, have PowerPoint presentations, but if you have something to say, we would like to listen. So think about that between now and then for any of you.

Ms. Brogdon?

MS. BROGDON: Could you clarify whether you mean five minutes per person or five minutes for the total feedback?

CHAIRMAN GLASSMAN: Per person, five minutes per person. I may, however, limit the number of people if it gets excessive.

We are going to move to Question C5, Sunder, if you could project that. We are going to go back to colon CAD.

EXECUTIVE SECRETARY WERSTO: Dr. Glassman.

CHAIRMAN GLASSMAN: Oh, I forgot. We have another break. Dr. Nick Petrick is going to present some

slides on some statistical analysis issues. That is what happens when I don't write things down.

DR. PETRICK: I am going to present just a couple of slides, a quick presentation. I just wanted to make a clarification about studies.

I had separated the sensitivity/specificity endpoints from the ROC endpoints. I just wanted to say that it may be important in certain clinical studies to look at the actual clinical decisions that are made, as well as trying to look at how the overall technology may impact clinical practice.

So it is actually possible to obtain both the ranking or rating as well as the action item within the same read or study. So I just wanted to make sure the Panel is aware of that.

So it is not necessary to make just a one or the other decision on sensitivity/specificity or ROC type of measures. You can just think of it -- you know, if it is clinical, it may be appropriate to determine whether the patient should have work-up or not as being the clinical decision and then have the patient rated on some suspicion level, or it could be that you make the

suspicion level decision on individual lesions and then determine the individual lesions that require work-up.

Go ahead to the next one.

Just an example from the literature; this is from Jiang. The author studied ROC curves, ROC areas and sensitivity/specificity operating points for the characterization of microcalcifications as malignant and benign. So this is just a curve you can get.

So you can actually get data on the whole ROC curve as well as individual operating points for a multi-reader, multi-case study design, and it could be either prospective or retrospective, the way you do these studies.

So I just wanted to clarify that for the Panel. Thank you.

CHAIRMAN GLASSMAN: Thank you, Dr. Petrick. Does anyone have a question for Dr. Petrick about what he just presented? Dr. Bourland?

DR. BOURLAND: I have one question, and it relates to the data that you show here, which is one point per curve and then a tracing of the curve.

So I realize they are essentially well

behaved curves, but I just want to make sure because we had a comment yesterday about how can you recognize an ROC curve that, for instance, is typical or not realistic.

So can you comment just briefly on the basically delineation of an ROC curve based on one data point?

DR. PETRICK: Based on one data point? This is an example of actually a case where you have increased sensitivity as well as increased specificity. So you are actually moving this direction on the ROC curve.

So in this case, just based on a single operating point, you can conclude that this is a better -- you have to have moved to a better ROC curve.

DR. BOURLAND: That, I understand. I'm talking about the shape of the ROC curve, going through that point and how well that can be done based on a single data point.

DR. PETRICK: Well, so the shape of the ROC curve is going to have to become -- it will have to be a convex curve like this. If it is chance, it is going to go along this particular axis. The curves typically will

always increase in sensitivity for specificity so you won't have dips or concavity in the curve. That would be an atypical ROC curve.

We also have to keep in mind that there are parametric ways of assessing ROC and nonparametric ways. Parametric curves will be a fitted model to the curve, where a nonparametric curve is taking that raw data and plotting it out.

You can do a statistical assessment based on that. Both have their advantages and potential disadvantages that go with it.

CHAIRMAN GLASSMAN: Dr. Carrino, you had a question?

DR. CARRINO: Yes, just with ROC methodology in general, measuring the whole area versus partial areas because I think we are going to get into problems where you could have -- you know, not have significant differences in the ROC curve but really have two differences and even vice versa.

DR. PETRICK: Certainly, what the appropriate endpoint, again -- that's a question for the Panel to come up with. Partial area is appropriate in

some situations potentially. We can look at the whole area. If all the operators operate in one particular location, then partial area certainly is an option to use as an endpoint.

Again, what is the clinical implication of that? What is the right endpoint? That is something for the Panel to discuss and try to decide on.

CHAIRMAN GLASSMAN: Dr. Berry.

DR. BERRY: So just to clarify, this is an example, and the differences are huge, converting a non-test into something that is valuable. This is illustrative and not real. Is that correct?

DR. PETRICK: Well, this is a real study that was done. It was a retrospective one that's presented in the literature on a microcalcification, determining malignant from benign microcalcification. So this is a real example from the literature. This is a particular real test.

Certainly, every test may not show -- Every CAD -- certainly, a detection CAD may not show such a big change in ROC area or sensitivity/specificity endpoints.

DR. BERRY: Okay. I mean, this changes my

view of CAD, if this were typical.

DR. PETRICK: Again, we are talking -- This is a diagnostic CAD from a research institution. So we are not talking about necessarily a commercial CAD. This is a diagnostic device as opposed to a detection device. But this is from the literature, and this is a retrospective study.

DR. BERRY: It doesn't come with standard errors or something to -- sample size?

DR. PETRICK: There is, I think -- I have to go back and look at this particular example, but I'm fairly sure that this would have come with a statistical significant analysis that came with these curves in the particular manuscript.

CHAIRMAN GLASSMAN: Thank you, Dr. Berry. Dr. Abbey?

DR. ABBEY: Just one quick clarification. Those curves aren't fitted to the one observed sensitivity and specificity.

DR. PETRICK: No, right.

DR. ABBEY: I wanted to clarify that from earlier. Those are separately estimated.

DR. PETRICK: Right. This study was give a ranking, and then provide the clinical decision that you made, in this case biopsy/non-biopsy or malignant/benign, a binary decision.

So there are two endpoints. One is the binary decision. One is the rating. And it is possible those could be merged together in some studies, but that's a study design issue.

CHAIRMAN GLASSMAN: Thank you, Dr. Petrick. Oh, Dr. Dodd?

DR. DODD: Well, while we are clarifying a few things, I want to clarify some things that I thought were implicit yesterday, just three points quickly. I thought it would be good to go on the record.

First of all, with regard to ROC analysis, I think everybody would agree that three points is not enough to fit an ROC curve. So if the C-Rad scale has three points, clearly you need to push toward something else for ROC analysis.

Also, we moved to a discussion of per lesion analysis and FROC, and I had assumed that people would consider correlation of the lesions in any analysis.

Technically, when we do that, I think we should be talking about JFROC, which is jack-knife FROC rather than FROC, because I think the original paper of FROC didn't consider correlation.

So we need to consider correlation whenever we have multiple lesions per patient or multiple sites per patient. That is also true whenever we have multiple lesions when we are analyzing sensitivity and specificity.

Finally, with regard to ground truth, I know we moved toward allowing repeat CTC for the negative scans, and while this is less than perfect, I recognize the limitations of being able to do colonoscopy on all the negatives or some proportion of negatives. But I do think the labeling will need to clearly state how truth is defined and what sensitivity and specificity are defined with respect to.

CHAIRMAN GLASSMAN: Thank you, and thank you, Dr. Petrick.

Okay, let's move on now to question C5 please, Sunder.

Please discuss whether there are other types

of performance testing -- that is, other than stand-alone or reader -- that you believe should be considered in the clinical evaluation of colon CAD.

Dr. Abbey, why don't you start, if you have any ideas or none?

DR. ABBEY: Not much. I would just say one thing. When we look for a lot of these comparisons between standalone and reader studies, the assumption is that there is some interaction that happens when you go to the reader study that causes the standalone not to really be predictive of the reader study.

It seems to me there may be less burdensome, more efficient designs to actually just assess that interaction rather than doing a full study, and I don't know what they are, but my sense is when you limit your scope, you can do something easier and put it out to statisticians then.

CHAIRMAN GLASSMAN: Any other comments about this one or is the sense of the Panel that there are no other testing that we would recommend?

Ms. Brogdon, the sense of the Panel is that there are no other tests other than standalone and

reader.

MS. BROGDON: Let me just ask the staff whether they possibly had anything else in mind?

CHAIRMAN GLASSMAN: Thank you.

MS. BROGDON: No, that's it.

CHAIRMAN GLASSMAN: Thank you very much. C6, please.

Please provide comments on the practice of using an enriched dataset for the clinical evaluation testing discussed in 3 through 5; that is, standalone and reader and no others.

If you believe that the enriched dataset may be used for these evaluations, please discuss what you believe to be the appropriate clinical and radiographic characteristics (or range of characteristics) for that database. Please consider such items as proportion of patients having polyps; proportion of patients having multiple polyps; and polyp size. And if you believe that enrichment is inappropriate, please provide your reasons and whether there would be an alternative method of assessing these devices.

Now some of these things, I think, we

discussed yesterday, but we have to specifically restate what we believed yesterday for things like polyp size. So who would like to start with this one? Dr. Berry? Thank you.

DR. BERRY: I think the issues are the same -- almost the same as in mammography, and I think we should make the same conclusion as in mammography, that enrichment is a fine thing and the same issues apply there.

There is a bit of a difference that I think Dr. Lin pointed out; that whereas, in mammography there is less than one percent prevalence in any particular test, here there is something like five percent prevalence of polyps.

So an actual clinical practice setting would be quite feasible. That could be, I think, enhanced with enrichment and the same issues that we discussed yesterday apply, in my opinion.

CHAIRMAN GLASSMAN: Dr. Lin?

DR. LIN: I think I would agree with that. It is really a question of prevalence, and if you take 100 average risk people being screened for colon cancer,

about five of them will have large polyps, and about 20-25 of them will have small polyps, smaller than one centimeter.

So it kind of depends on how large these studies are anticipated to be. If the studies are going to have less than 500 subjects, then enrichment might be necessary, but if the studies are much larger than that, then we might be able to have enough patients with polyps without using enrichment. But I anticipate that the studies are probably going to be less than 500 subjects.

CHAIRMAN GLASSMAN: What about multiple polyps?

DR. LIN: I'm not sure if multiple polyps is really going to be such an important factor in this. I'm not sure what other people feel.

CHAIRMAN GLASSMAN: Anyone else? Dr. Wong?

DR. WONG: I think when you are looking at standalone, you want to really enrich the population. I don't think you lose anything because basically you are running the CAD through a standalone process.

So I would think that you would want to enrich it with various size polyps, most likely greater

than 6 millimeters. Obviously, you want to get polyps over 10 millimeters because that is the key polyp size, but you want to see how sensitive your CAD is in terms of finding polyps between 6 and 10 millimeters.

I think that you want to have polyps throughout the colon, and you want to have it in the various sites we have talked about, in the flexures, in difficult places because you don't want to miss those types of polyps in people.

So I think, for the standalone, you would want to do that. For the second reader, you know as we said, if you enrich too much, then you are going to have a problem there in the sense that the person who is reading it is going to be sort of hyped up to expect polyps. So I think, in that sense, you may want to change it.

CHAIRMAN GLASSMAN: Dr. Rosenberg?

DR. ROSENBERG: One reason for enrichment is to make the testing more efficient. It will take less time. So a question I have for the Panel is: how many subjects are we talking about and how long does it take for each study to be read so there is a way of knowing

how long this process would take?

In other words, what kind of resources are involved?

DR. KIM: I think a reasonable estimate in terms of how long the study takes -- there is a big range. People say they can get down to 10 minutes. Some people say it's 45 minutes, but I think a reasonable estimate probably to get through a study is about 20 minutes.

To do more than 15 in one day is a pretty long day. So number-wise, it is going to be kind of hard to get big numbers like 500 or something like that.

CHAIRMAN GLASSMAN: What about stress testing with difficult cases such as flat polyps? Does that have a place in this CAD evaluation?

DR. TOURASSI: I believe that when we are talking about stress testing, that should be part of the standalone performance, and I want to reiterate the point that was made before that enrichment is indeed very important for CAD evaluation. But how we do enrichment should be different for the standalone performance versus the reader in the loop.

For the standalone, we can do anything we like. We can collect the same number of cases for a particular size or a particular type of abnormality and have the necessary statistics, and all that is critical information to be conveyed to the end user before they start using the system. But when we put the user in the loop to do the reader observer studies, we should do enrichment, but we need to make sure that the different substrata in the abnormal cases reflect the overall prevalence in the actual population.

DR. ROSENBERG: I would agree with that 100 percent.

CHAIRMAN GLASSMAN: Any other comments? Dr. Berry?

DR. BERRY: Just a point about Dr. Kim's 15 in one day is a lot. A typical study here, I would think, if it is a registration trial, would have multi-centers and if it is standard clinical practice, I could imagine that there could be more than 1,000 -- you know, in the thousands, and it wouldn't be a terribly expensive trial, I would imagine.

CHAIRMAN GLASSMAN: Dr. Abbey?

DR. ABBEY: I was going to go the other way. At 20 minutes per image and five percent prevalence, I don't see how you can do it without enrichment without putting a huge burden on whoever has to do that study.

CHAIRMAN GLASSMAN: Dr. Berry?

DR. BERRY: No, but the point is that there will be potentially 50 centers that are accruing patients.

CHAIRMAN GLASSMAN: Under the least burdensome doctrine -- let's split this into two clearly defined pieces -- the standalone where the burden to the companies is really relatively minor once cases are identified, and the reader study where the burden to the company is much greater.

I think we have said that for the standalone, that any -- we could do significant enrichment and stress, but for the reader study, do we think that thousands of patients would be necessary to evaluate a CAD system?

DR. SAHINER: I think when we are doing a reader study, we also want to sample the readers. So these cases will be read at -- you said there will be

multiple centers, but every case would have to be read in multiple centers, too.

So I think it would be very difficult to conduct this study with 1,000 cases or thousands of cases.

CHAIRMAN GLASSMAN: Does anyone want to hazard -- Oh, Dr. Bourland first.

DR. BOURLAND: You should continue. I had a slightly different topic.

CHAIRMAN GLASSMAN: So did I. So go ahead.

DR. BOURLAND: So I wanted to just point out that, relative to detection of items with CAD colon, it is sphericity that is detected. So these are all designed -- the current approved ones are basically designed for polyp detection. So the flat lesion is a non-detectable because there is no curvature to detect mathematically within the image set.

So the question is what about enrichment of something like that? There are not at this point systems really designed for that purpose. So that is a very difficult case, and the question is do you enrich for something like that or not when perhaps the systems

aren't actually designed to be able to detect the gently rolling hill as opposed to the complete 180/360 degree curvature change.

CHAIRMAN GLASSMAN: I'd like to respond to that, and I think the answer is that as part of the stress, we should look for that. The reason is that it would be important in the labeling for the end users to know that that is an area where this test is insensitive if in fact, it is insensitive.

DR. BERRY: Can I add?

CHAIRMAN GLASSMAN: Yes, Dr. Berry.

DR. BERRY: I would say that there is a distinction between enrichment and ordinary practice. In ordinary practice, that would come up and one could add something in the label, but the overall performance of the device should be calculated on the basis of how it does overall in a representative sample; and if those are common, then the device is not going to be as good as if they are quite rare.

CHAIRMAN GLASSMAN: Thank you.

DR. SPINDELL: Could I add one comment?

CHAIRMAN GLASSMAN: Of course.

DR. SPINDELL: Your comment is exactly right. How does it act in real life? Just so everybody understands if you are enriching the reader sample, that's not real life.

CHAIRMAN GLASSMAN: However, I think statistically we could make -- or someone could make a judgment based on a real world population, taking out the unrealistic cases once we know that it doesn't work for those, and simply label to say that flat polyps are dangerous, this system isn't going to find them. So you have to be aware of that, and then a reasonable sensitivity and specificity based on usual clinical practice could be obtained.

Yes, Brian? Dr. Garra?

DR. GARRA: I just have one comment about that. I think you are right about possibly needing a sufficient sample of sessile polyps and flat polyps, but only if their proposed labeling suggests that they think they can detect them. If the proposed labeling for that device is that we can't detect those, then I don't think that we should put that burden on them.

CHAIRMAN GLASSMAN: I think that is

reasonable because it would then -- the label would then tell the end user what we, in fact, want them to know. Dr. Berry?

DR. BERRY: But they should be included in any calculations of sensitivity and specificity, despite what the label claims. That is, if you can't find it, that's not a good thing.

DR. GARRA: I think that's fine to do that, but I don't think we should enrich or force them to have a certain number of flat polyps if they are not having that in their label.

DR. BERRY: I agree.

CHAIRMAN GLASSMAN: Dr. Dodd?

DR. DODD: I just want to agree with Dr. Berry, and I do -- again, we are making a distinction between the standalone enrichment and the type of enrichment that is done with the reader performance study, right?

So I would also hope that you get some sampling of them for a reader performance study, but that you don't necessarily have to enrich on that specific criteria. But I would be very hesitant to throw those

out because those should be part of your estimates of sensitivity and specificity.

CHAIRMAN GLASSMAN: Dr. Rosenberg?

DR. ROSENBERG: If we are going to talk about that, then we are going to have a problem with verification of negatives, of people only done by CT.

CHAIRMAN GLASSMAN: Thank you.

DR. ROSENBERG; I asked about that. I am not clear on if it's a flat polyp, whether a colonoscopy is going to find it?

CHAIRMAN GLASSMAN: It should. Dr. Lin?

DR. LIN: Flat polyps are traditionally more difficult to diagnose than pedunculated polyps, but I think in general colonoscopy has a better chance of finding flat polyps because we can actually directly view the mucosa.

So yes, they are difficult to find on colonoscopy but probably less so than with virtual colonoscopy, and CAD I think, it would be very difficult because of the reasons that you just mentioned.

CHAIRMAN GLASSMAN: Let me just switch gears a little bit here for one second just to make sure we

cover this, and go to b. Is there anyone on the Panel who thinks that enrichment is inappropriate? Okay, we've answered that.

Let's go back then to a. and let me try to summarize where we are and then open it back up for discussion.

We have separated the standalone study from the reader study. For the standalone study, the committee -- we believe that enrichment and stress is appropriate. For the reader study, we also believe that it is appropriate but at a lesser level to better reflect clinical practice.

The actual proportion of polyps we haven't specified, but I don't know that we can. Multiple polyps, we said, would not be particularly important; however, polyps in all areas of the colon needed to be included including the problem areas of the flexures, and that polyps between 6 and 10 millimeters and greater than 10 millimeters needed to be included in an adequate test.

Let me open it up again for comments if there is anything anyone wants to modify of that or further enhance. If not, Ms. Brogdon, I hope somebody

took notes on that.

MS. BROGDON: Yes, thank you.

CHAIRMAN GLASSMAN: That is adequate for what you need?

MS. BROGDON: Yes.

CHAIRMAN GLASSMAN: Thank you. We are doing well this morning. Let's move on to C7.

FDA does not specify indications for use but reviews indications for use that are requested by companies. What are the Panel's views regarding second reader versus concurrent reading using a CAD device?

Specifically, how are colon CADs used clinically? Are second reader and concurrent reading modes both clinically relevant options for use in practice? If not, which paradigms are appropriate for colon CAD devices?

Do you believe users understand that if a device is labeled as a second reader, they the physician, should always read the radiological image completely before turning to the CAD?

At this point, as I mentioned earlier, I would like to ask if there is anyone in the audience who

would like to speak, particularly to Section a., but if you have something to say about b. or c. within your five minutes, that would be fine.

Is there anyone who wants to make a statement? Please raise your hand and come forward. No? Okay, then we will continue on with the Panel's discussion. Thank you.

How are colon CADs -- Oh, there is someone? Oh, please come forward. I'm sorry. I had my reading glasses on. I can't see past the podium.

Please state your name and any affiliations that you have, please.

MR. TRUYEN: Good morning. My name is Roel Truyen. I am at Philips Healthcare.

Now just as a remark on the clinical use, I am not a doctor, by the way. So I don't use these CAD systems in real practice.

With respect to the question whether or not this is being used in a concurrent read or a second read paradigm, I think both options should be available if the device manufacturer decides to put it in their labeling and their claims.

So if you will have a device that is intended to be used as a second read, that is appropriate; and then it should be tested in the reader paradigm that it is intended for. You can also have a reader paradigm that is a concurrent read so we don't exclude these devices. In that case, they should be tested in that way.

What we would not like to propose is to have labeling for one reader paradigm and then having to test that for other reader paradigms that it was not intended for.

CHAIRMAN GLASSMAN: Thank you very much. Any -- Yes, sir? Come forward.

DR. JAFFE: Carl Jaffe, NCI Cancer Imaging Program. We were the sponsors of the ACRIN trial which has come to completion just for some benchmarks on these things so that they can be cited for later literature.

That trial has 2600 cases in it. It cost $6 million. It was completed in less than two years. It has not yet been published, but it is in the process of doing so. Some of the secondary endpoints include the issue of primary first read versus second read situation.

So I think the Panel should be aware that within the literature, within the next 18 months to two years, there will be the publication of information.

This was a 15-site, multi-center, multi-institutional and multi-device, and visualization software. It was not a CAD driven project. This should allow people to have a little bit of understanding. It is very well, scientifically controlled, biostatistically.

So this will, I think, provide some background when this is looked at later. Thank you.

CHAIRMAN GLASSMAN: Thank you, Dr. Jaffe. Yes, ma'am?

DR. SALLAM: I am Maha Sallam from iCAD. I just wanted to ask the Panel as you considered the issues of concurrent read versus second read and the potential scenarios, try and also make recommendations on the testing and whether that differs or should differ, whether the intended use of the device is a second read device or a concurrent read.

It is overly burdensome, I think, for industry to try and prove or disprove all different

methodologies that a particular device can be used for. I think it is appropriate for us to propose a recommended methodology for the use of our device, based on our knowledge of what it does and does not do, and then allow us a design testing that is proportionate or suitable for the type of utility or utilization that we are expecting our device will be used for. Thanks.

CHAIRMAN GLASSMAN: Thank you. Any other? We have no one else who wishes to speak. We will move on to --

DR. BERRY: May I ask a question?

CHAIRMAN GLASSMAN: Oh, I'm sorry. Yes, Dr. Berry?

DR. BERRY: So I would like to ask Dr. Jaffe with respect to Dr. Sallam's question just now, how did you do the ACRIN trial? If you are going to compare concurrent versus second read, how did you do that because that is a different design than we have been talking about?

DR. JAFFE: These are secondary analyses, and again we are just simply the sponsor. ACRIN's protocol for all of this is actually up on the web on

their site. The issues that you are addressing are actually the -- are not primary aims. They are secondary aims, and they will be -- presumably, they will be finished -- that analysis is a reanalysis of the dataset that comes from that.

Portions of that dataset will become publicly available so they could be used as a test.

DR. BERRY: So just crossly, did you have different readers, one reader doing things concurrently, and then on the same case another reader doing it sequentially?

DR. JAFFE: I think that will have to be answered by the principal investigator, which is Dan Johnson at Mayo Clinic, but my understanding is that it is not really so much concurrent as primary first 2D, secondary 3D and then the reverse after a forgetting period.

So you will get some information of that, not precisely what you are asking about concurrent, but there will be a very rich amount of data here that can be used as a potential benchmark, although I would say it is not for CAD. It is visualization issues, 3D. Thank you.

CHAIRMAN GLASSMAN: Thanks, Dr. Jaffe. Yes?

DR. SPINDELL: Dr. Jaffe, sorry. The CAD product that was used, multiple CAD products -- were they --

DR. JAFFE: Oh, I'm sorry. It was not CAD. Visualization products -- they were helpful.

DR. SPINDELL: And were they used on their indicated use? Were those devices also indicated for primary read or just indicated for secondary read?

DR. JAFFE: I'm afraid I would have to look that up, but it was, as I say, 15 institutions nationwide, 2600 cases with multiple scanners and multiple visualization devices, the 3D visual.

DR. SPINDELL: The reason I'm asking is I just want to make sure that, when somebody interprets the study that the data is relative to the indicated use for the device and not for non-indicated use for the device.

DR. JAFFE: Again, it is a visualization issue, and it was -- my understanding is that it is licensed devices. I just thought it was also useful to have this cost benchmark which was that for 2600 cases. It cost $6 million of NCI funds. Thank you.

CHAIRMAN GLASSMAN: Thank you very much.

Okay. Let's move on to the Panel's discussion of C7. How are colon CADs used clinically?

I can tell you from my own observation that they are used both concurrently and sequentially. People I have spoken to prefer actually the sequential. The comments I have gotten are the marks get in the way when you are flying through the colon on a 3D fly-through, and then they go through again looking for the marks, but I don't know what the rest of the Panel's knowledge is.

So why don't we open it up for discussion of the three points. Who would like to go first? Dr. Kim? I'm sorry, Dr. Leitch.

DR. LEITCH: Well, I don't know how people use this, but I think this exam where it takes a lot of time to do it, you know, just to view the exam, this will be something that in practical use there may be the inclination to either have the CAD system do the primary read or to do concurrent reads.

So I think, while the company can say well, we are not going to promote it that way, we are not going to say that is the indication, I think the issues are in

practice if that's what will happen, that needs to be addressed in some way.

CHAIRMAN GLASSMAN: Let me make a comment about that. That is, if I understand this correctly -- and FDA people, please correct me if I'm wrong, but the FDA evaluates the stated uses that come from the company. So if the company comes to the FDA with a second use product, that that is what the company has to prove.

If the company comes with a concurrent use product, they would have to prove that; and if they come for both, they would have to prove both. But the FDA responds to the submission rather than the other way around. Is that correct?

MS. BROGDON: That is generally correct. If you think of other devices where there are obvious potential off-label uses that we believe could be hazardous, we can reflect that in the type of clearance and warnings that we give with those approvals.

I don't believe we are talking about that here so what you said is correct.

CHAIRMAN GLASSMAN: Thank you.

DR. LEITCH: I understand that principle,

but these are concerns that I have about this. Is that because it is a time consuming procedure -- and again this is the issue? You know, if it is going to be applied in screening, how will it actually, practically, be use?

This is one of the questions asked: How are they used? Maybe people who have more experience in the area can say what do they think people are likely to do or what would they rely on? Would they tend to rush through their first read, knowing they've got that back-up read? How would it happen, actually, in real life?

CHAIRMAN GLASSMAN: Dr. Swerdlow, any comment on that?

DR. SWERDLOW: I don't have a CAD available. So I can't say how I use it at the moment; and as I have indicated, I think I would certainly love to see something that would work as a concurrent read because of the potential for large numbers of cases that people are going to have to read.

I think that is going to prove a strong market drive, that anybody who can -- that any manufacturer that can make one of these and show that it

actually works as a concurrent read will have a big leg up.

That is going to drive somebody actually seeking to get to approval of that, and that may in itself be sufficient to spur industry in that direction.

CHAIRMAN GLASSMAN: But for the FDA purposes, I think the answer is it is being used clinically both ways right now, based on?

DR. SWERDLOW: That is my impression, but I have a fairly limited orientation with what others are doing.

CHAIRMAN GLASSMAN: Anybody else want to speak to a? Let's move on then to b., which is somewhat related, which is -- are second reader and concurrent reads both clinically relevant options; and if not, which one is?

Is there anyone on the Panel who thinks that both of them are not potentially clinically relevant? Dr. Garra?

DR. GARRA: I did want to raise the issue of -- I think they both are clinically relevant, but the more important question is: If a device purports to want

to do both concurrent read and second read, do we need to make them test both? Can we just make them test concurrent read because everything I have heard from this Panel so far is that concurrent read has a potential for lesser performance? So that would be the higher bar.

If they could pass the concurrent read, then the presumption would be that the second read performance would be higher. I am just curious about that, what the Panel feels.

CHAIRMAN GLASSMAN: That is a very important question.

DR. GARRA: It reduces the burden for them considerably.

CHAIRMAN GLASSMAN: Exactly. Does anyone want to speak to the fact that if a device is approved for concurrent read, this Panel would recommend that it, by definition, be also approved for sequential read for the reasons that Dr. Garra stated?

DR. LIN: I think theoretically it does make sense, but I don't think there is any actual proof that that is a higher bar, though. Intuitively, it would seem to make sense that, if a CAD could perform well for

concurrent reading, that for second reading it should do even better. But is there any actual events?

CHAIRMAN GLASSMAN: Dr. Tourassi?

DR. TOURASSI: Actually, I agree with that. In principle, it's right, but we also need to consider any future paradigms, reading paradigms that we cannot envision right now.

So the real question is: If the sponsor comes in with a proposal of another reading paradigm, do we require a new reader observer study comparing the new reader paradigm to the previous paradigm? This is a real question, and under the least burdensome approach very difficult to give an answer.

CHAIRMAN GLASSMAN: Dr. Bourland?

DR. BOURLAND: We heard briefly about the use of visualization for this, which essentially is taking the CT and perhaps doing a fly-through. So the question is where does CAD start? Where does visualization end?

I don't know that I know the answer to that. You can imagine a situation where the visualization uses, for instance, the heated object spectrum, and that is the

first view that is taken of this dataset in a represented view of some sort.

The heated object spectrum would show, for instance curvature, and your eye would go right to that, and that tells you almost right away that is a potential polyp, for instance.

So I am a little unclear, unsure, of how a vendor implementation might link visualization to CAD. To me, they are probably integrated right now such that -- and what I am suggesting is that the first view you ever see is sort of -- it's visualization, but at the same time it is a concurrent observation.

CHAIRMAN GLASSMAN: Dr. Berry?

DR. BERRY: So following onto Dr. Tourassi's comment and Dr. Garra's, I thought I heard Dr. Garra say that if a device is approved indicated for second read, that it might be used in the concurrent setting; and therefore, it is incumbent on the company to evaluate it in the concurrent setting.

CHAIRMAN GLASSMAN: No, he actually said the reverse, I think.

DR. BERRY: Okay. Well, let's ask him.

CHAIRMAN GLASSMAN: Okay.

DR. GARRA: The issue here was -- I think if a company goes in and says our device we want only to be used for second read, then that's what they would be testing. But if a company says, we would like our device to be approved for both second read and concurrent read, would the FDA require them to test them both?

Since all the discussion I have heard here indicates that there is greater potential for problems with performance with concurrent read versus second read, it might be an easier burden for them to just do the concurrent read, and then be approved for both if they have that indication.

DR. BERRY: So let me raise the question then. If it is approved only -- or cleared for second read, is it incumbent on the company to show -- to evaluate what its performance is in the concurrent setting?

DR. SPINDELL: I think we already discussed with the FDA that the FDA -- that is not the burden of proof for the company. The company has to prove their device is safe and effective unless that other read is

extremely dangerous.

I also think you have to understand when you do testing for clinical off-label and as part of your submission, as you know, it's now on the clinical database and everybody gets information that could actually promote off-label use rather than deter it. So I think you have to take that into consideration as well.

CHAIRMAN GLASSMAN: Okay. Yes, Dr. Abbey?

DR. ABBEY: I just have a question. How do you know it is extremely -- if it is extremely dangerous or not, unless you test for it?

DR. SPINDELL: I think what you have to understand is what is the possible -- let's take CAD in particular. Right? What is the danger in the CAD? What is the danger you are trying to prevent here?

DR. ABBEY: In off-label use, wouldn't that be that it is being used inappropriately; and therefore, sensitivity goes down and a certain number of people end up --

DR. SPINDELL: But if you could put that in your package labeling is what I'm saying, is if you have a second read device, you say in your package labeling it

is a second read device, not to be used concurrently, sensitivity and specificity is not --

CHAIRMAN GLASSMAN: We are into a risk management issue here which is not part of our purview. The general way that this works, as we all know, is that the company comes with an intended use and they have tested for that use. And the label says that that is the use that it should be, and anything else is not there. Then people use it as they will.

Let me see if I can -- the third part -- do you believe that users understand that they should only use it the way the label reads? Dr. Wong is shaking his head no.

DR. WONG: No, I don't think so. I think people are going to use it the way they want to use it. So, actually, it comes back to this other question, and that is, maybe we should ask the companies to look at concurrent use because more than likely, because this is such a time consuming read, that they are going to use the CAD to try and save time. I think that's the most common likely thing that is going to happen.

I may be reading it wrong because I'm a

gastroenterologist, but I would think, if anything, they are going to try and save time and be able to read more cases using the CAD.

So maybe the best thing to do is to see whether the device companies can show that concurrent use is as good as a person reading it, and make that as a --

CHAIRMAN GLASSMAN: I think -- Well, I think there are certain assumptions we are making here, and with colon CAD it may not be true that concurrent CAD is faster than sequential CAD.

I have been told by one user that sequential is actually faster because as you fly through the colon, if you -- It's like a street with stop signs versus -- I was going to say 270, but some days that is like a stop sign, too. But 270 at two in the morning, and that when you go through and you have to stop and check and stop and check and start again, it is actually slower.

So I don't think that in this instance we can assume that concurrent would be preferable to sequential.

DR. KIM: I think, in terms of time, there is one study. I'm not sure if it was Steve Halligan or

Stuart Taylor that led the study, but they looked at both concurrent read and sequential read, and the reading times for concurrent read were much quicker than the sequential.

DR. SAHINER: I have one comment about the question of whether the users understand what the labeling says. I think they understand, but they may forget.

So one easy strategy to discourage the off-label use for these software devices is just to ask the radiologist before you turn on the CAD whether the user has read the image completely or not.

So this would be not that big a burden on the radiologist. They would just click a button, and it would remind them each time not to do the off-label use.

CHAIRMAN GLASSMAN: I don't necessarily think that that is the function of the FDA. Any other comments before I try --

DR. TOURASSI: And also human nature. Most probably they will push the button anyway.

CHAIRMAN GLASSMAN: Yes. Dr. D'Orsi?

DR. D'ORSI: Is there a richness of data to

compare CAD and non-CAD paradigms, as there is in mammo, to make a decision on this? Do we have enough info that we can say one is preferable to the other?

Maybe we should just kind of leave it open to fit what data we have now. I don't know, but is it available? I mean, we have tons of data with mammo. I don't know if there is similar data with the CAD for colon.

CHAIRMAN GLASSMAN: I don't think that there is the richness -- or there isn't the richness of data. It is a much less researched area, and I think that is part of why we are taking so long with this piece is that we don't have the data to really back up.

One more comment. Then I am going to try to summarize.

DR. CARRINO: So I think the fundamental issue is not the time, but is concurrent use similar enough to second reader use that they can be tested equivalently?

So we have the three paradigms that were put forth yesterday which was the completely standalone device, concurrent, or second reader paradigm where the

device is applied after the radiologist has gone through the image.

So from a concurrent use standpoint, a number of radiologists will go through a case. To me, that seems that that could be like a second reader scenario, because you are going through the case anyway, and these marks are there. Whether you apply them before you started looking at the case or after you have looked at the case, it's roughly similar.

What is not clear to me is that a second reader paradigm is the same as the concurrent use paradigm because then you have gone through the whole case, made your opinion, and then you apply this device.

So I think that if we are going to try to make it least burdensome, that we can decide that concurrent use is similar enough to second read, then that's the way that you have the testing done.

CHAIRMAN GLASSMAN: Any other comments about that? My one -- Oh, go ahead.

DR. STEIER: Just one comment. We have heard a lot of the speakers yesterday talk about the importance of second reader use, and the FDA staff and

others all made it very clear that this methodology should only be used for second reader use. So it is interesting to hear so many people advocating for concurrent use.

CHAIRMAN GLASSMAN: I would like to suggest to the Panel that, in the absence of comparative data, that we should not make any recommendation about the equivalence of second read and concurrent read, that the industry can apply for what they want with the data. The FDA will evaluate it, and it may be in the future that, when scientific data shows different facts, this can be changed.

Would that be acceptable to everybody? Okay.

Let me try to summarize C7, and then we will open it back up for discussion, and then we will come to a final.

How are colon CADs used? They are used both sequentially and concurrently at this time.

Are second reader and concurrent reading modes both clinically relevant options? I think we agree that they are clinically relevant, but there is no

scientific or not enough scientific data to show that they are either equivalent or one is better than the other.

Do users understand that if a device is labeled for second reader and they should always read before turning on CAD? If they understand, they certainly don't always obey which is typical for the medical profession in general.

I think it is very similar to the issue with breast. Labeling could be made stronger. Teaching -- using the paradigm that we used earlier yesterday, that teaching of use could stress the proper labeling, but in the end people will do what they think works in the absence of scientific evidence to the reverse.

Let me open that up to the Panel. Would anyone want to modify that or add to it? If not -- oh, Dr. Tourassi?

DR. TOURASSI: I don't want to modify. I want to throw in a hypothetical scenario.

So let's say a colon CAD device has been approved as a second reader, and a future version of the device has been developed where sensitivity and

specificity have improved, and the sponsor feels that now the device is ready for concurrent read paradigm.

What do they need to do? They need to come back with another reader observer study to demonstrate what? That it is better or equivalent to the second reader as before? Furthermore, should this reader observer study be at the same scale, sizewise, number of cases, readers, as the previous one?

CHAIRMAN GLASSMAN: If I can respond to that, I think that the answer may be yes and may be no, depending on the state of scientific evidence independent of that trial. If there is massive literature support that the two were equivalent, it may be that the reader study that would be acceptable to the FDA would be of a different size than if this were, in effect, a new paradigm to be tested.

DR. STEIER: I would like to respond to the statement that you made. I agree with most of it, just the last part about people will do whatever they think is right based on however they feel that day or what works for them.

I don't know that that really adds a lot. I

think, if it is approved as a second reader, like all things, it should be used for what it is approved for, and I guess it goes unsaid most of the time that physicians will comply to the extent that they feel that they need to or it is indicated. But I don't know that giving an out in terms of including human nature in our statement is that necessary.

CHAIRMAN GLASSMAN: We can drop that from the last part. Ms. Brogdon?

MS. BROGDON: I guess one of the things we are asking is if you believe that there is commonly done off-label use, what does that say about the labeling?

Do the people who are using these devices off-label need further labeling, either to prevent, give adverse information about what they are doing, or positive information about the results that they can expect if they are using it off-label?

CHAIRMAN GLASSMAN: Anyone want to comment?

DR. STEIER: Well, again I mentioned yesterday from the cardiology and pulmonary viewpoint where in cardiology EKGs are read by machines, and you can either read them yourself or go with what the machine

says and then kind of concurrently read it or for pulmonary function testing you can do that. It is considered poor practice to use the machine interpretations as opposed to the physician interpretation.

CHAIRMAN GLASSMAN: I think also, to answer your question, that labeling and training could be made stronger but, quite frankly, in the absence of scientific evidence showing that second read is worse than concurrent read in CT colonography with CAD, it would be hard, I think, to make a real significant impact.

Yes, Dr. Abbey?

DR. ABBEY: So I guess there is a lot of off-label use of the drug Valium, but I think it says more about Valium than the label. Right? I think CAD has a similar issue in the sense that it is so easy potentially to use it off-label.

So that is the potential risk there. But the one mechanism we haven't really discussed is post-market approval kind of studies. Should that perhaps -- if people are going to extensively off-label use a product and that has a negative consequence, wouldn't

that show up in a post-market?

CHAIRMAN GLASSMAN: Ms. Brogdon, do you want to discuss the agency's post-market processes and uses?

MS. BROGDON: We are unable to require a post-approval study for an off-label use.

DR. STEIER: You mentioned Valium, for instance, although Valium is on our hospital formulary. We were unable to approve it or even discuss at our Pharmacy and Therapeutics Committee meetings off-label uses. So I think there is a difference between off-label use as physicians determine is necessary versus official sanctioning of off-label use.

CHAIRMAN GLASSMAN: Okay. I think the analogy was good, but we are not here to kill Valium or anything else here.

Okay. I think -- Oh, Dr. Garra?

DR. GARRA: I think that the FDA is going to need to require the device to give electric shocks to the person if they use it off-label.

CHAIRMAN GLASSMAN: I'm glad I don't do CT colonography CAD. Dr. Berry, and then we are going to close this out.

DR. BERRY: I just want to point out that in today's issue of JAMA there is a paper that claims that flat growths are both much more common than previously thought, and that flat growths give rise to colorectal cancer much more than non-flat, to your point.

CHAIRMAN GLASSMAN: Yes. Dr. Brogdon, do you need me to try to summarize this again or is what we have said enough for the agency?

DR. BROGDON: I think we have enough.

CHAIRMAN GLASSMAN: Thank you. Let's move to today's agenda.

We now have the 8:40 FDA presentation, highlighting current issues related to lung CADs. Dr. Sophie -- I hope I do this right -- Paquerault is going to present.

DR. PAQUERAULT: Good morning. That's all right.

So we will be discussing this morning lung CAD devices and in these presentations I will go through some clinical background, clinical interpretation of chest studies. I will give an overview of CAD devices for chest X-ray and chest CT, and finally give an outline

of issues specific to chest X-ray and CT lung CAD.

The clinical background: the question is how chest X-ray and chest CT CAD devices are used. To respond to this question, it is important to define when and why patients are referred for a chest examination.

X-ray and CT are the most common chest imaging examinations. They are used for hospitalized and non-hospitalized patients of all ages and for various conditions.

Chest X-ray and CT can reveal disease and abnormalities of the heart, lungs and airways and many other chest diseases and patient conditions.

Chest X-ray is the most commonly performed radiographic exam, accounting for nearly 50 percent of all imaging tests. Over 250 million chest X-rays are done yearly in the U.S.

They are routinely performed for -- to determine the cause of chest pain, shortness of breath, fever, and trauma, and also for screening for pulmonary metastases or monitoring cancer therapy.

Chest X-rays consist of two views, a PA view and a lateral view as shown here, and these two views

typically can help determine whether other tests are needed to confirm or make a diagnosis.

Most common additional imaging test to clarify chest X-ray findings or to search for abnormalities not visible on the chest X-ray is CT examination.

About 65 million of CT exams of all types are performed every year in the U.S. About 10 million are of the chest.

CT can detect much smaller and more subtle findings than can be seen in the chest X-ray and is more effective in finding earlier lung cancer.

CT also allows precise imaging guidance for biopsy of suspicious findings.

As shown here, CT produces hundreds of cross-sectional images of the chest that contain complex and detailed anatomic and pathologic information.

Among the diseases that can be detected on chest X-ray and CT, lung cancer is one of these diseases, and lung cancer accounts for more deaths than breast cancer, prostate cancer, and colon cancer combined.

The major causes of lung cancer are due to

smoking for 90 percent and due to occupational exposure for 10 percent. Eighty percent of lung cancer patients die from this disease.

It is hoped that early detection and new interventions may result in a more favorable prognosis, and for this a screening program in high risk patients is a topic of discussion in the medical field.

The question remains whether early interventions in high risk patients is sufficiently effective to justify screening large asymptomatic populations.

To respond to this question, there are ongoing clinical trials: the International Early Lung Cancer Action Project and the National Lung Screening Trial.

There is various multiple published studies involving high risk patients, and they show a great variation in lung cancer detection for chest CT. Sensitivity varies from 67 to 100 percent. Specificity varies from 50 percent to 95 percent.

Twenty-five percent to 50 percent of individuals undergoing chest CT will have a lung

abnormality, either malignant or benign. A positive finding results in additional radiation dose, invasive testing, and may lead to complications and certainly increased patient anxiety.

What is the appearance of lung cancer or pulmonary nodule? Early lung cancer typically appears as a nodule or mass-like opacity on both chest X-ray and CT.

On chest X-ray, a nodule is defined as a relatively spherical opacity 3 centimeters or less in diameter surrounded by lung parenchyma.

On chest CT, a nodule is defined as a round opacity, at least moderately well marginated and no greater than 3 centimeters in maximum diameter. A nodule is typically described as completely solid, partially solid, or non-solid.

What is the frequency of pulmonary nodules? Chest X-rays diagnose about 150,000 new cases of solitary pulmonary nodules each year in the U.S. This estimate does not account for all of the smaller nodules detected with CT, and the fact that many patients will have -- may have multiple nodules on the chest CT scans.

Therefore, the inclusion of the smaller nodules detected on CT would dramatically increase follow-up.

What is the assessment for pulmonary nodule? It is difficult to distinguish benign from malignant pulmonary nodules on imaging. And furthermore, a solitary pulmonary nodule may be secondary to one of a long list of differential diagnoses including neoplastic, inflammatory, congenital, and many others.

Pulmonary nodule management is directed by criteria on nodule size and characteristics. In a chest X-ray, patients with all non-calcified pulmonary nodules are referred to CT. In chest CT, nodules that are less than equal than 4 millimeters in size are generally disregarded for low risk patients.

For all patients, follow-up CT of nodules greater than 4 millimeters is recommended. Biopsy is recommended for polyps that increase in size over time or are greater than 8 millimeters.

The clinical interpretation of chest studies -- unlike mammography and CTC which are performed to identify a single disease, both chest X-ray and CT are

used to diagnose various chest diseases.

When interpreting chest X-ray or CT images, radiologists rely heavily on the reported signs and symptoms, other history, as well as comparisons to prior studies.

In all patients, chest X-ray and CT interpretation include evaluation of many structures in addition to the lung parenchyma.

Searching for lung nodules in a chest X-ray is a complex task similar to searching for cancer on a mammogram. Searching for lung nodules on a CT is relatively simple task but overly burdensome because of the large number of individual images.

Furthermore, patients with a solitary pulmonary nodule rarely have symptoms related to the nodule. So the detection is usually unexpected and made in the context of searching for many other findings.

Detection accuracy greatly varies with physician experience, nodule size and location, and on the X-ray acquisition technique or CT protocol. For example, radiologists fail to detect lung nodules in chest X-rays in up to 50 percent of cases in which

nodules are visible in retrospect.

This is a study by Rusinek that showed that sensitivity and specificity of pulmonary nodule detection using low dose CT is somewhat comparable to conventional CT but varies by nodule size, location, and vessel proximity.

This table shows that there is potential for detection improvement in all factors but more specifically, from small nodules, nodules located in the hilar or central lung, nodules adjacent to blood vessels.

Let me give you another view of CAD devices for chest X-ray and chest CT. Unlike CAD devices for mammography and CTC which are intended to detect the only disease revealed, CAD devices for chest X-ray and chest CT are intended to detect only one of the various diseases and conditions that may be revealed.

One of the abnormalities that chest X-ray and chest CT CAD devices can be designed to detect is solid pulmonary nodules. Like other CAD devices, it prompts to areas of the lung for physician consideration.

Various types of marks are indicators that can be used to prompt to the computer-identified regions.

Here is an example of a chest X-ray CAD prompt, and here an example for CT lung CAD prompt. As shown, it can be displayed on the slide, on the 2D slide. As well, the location can be also represented in a lung map, and 3D representations can be displayed also.

Because various normal structures look like nodules in chest images, a major challenge in chest CAD devices is to achieve a low number of false-positive results, and this is true for all other CAD devices.

Chest CAD devices have been reported with up to five false positives per view on a chest X-ray, up to 10 false positives per patient on a chest CT.

Because chest X-ray -- so here I would like to talk about the effect of CAD on physician interpretation. Because chest X-ray and CT exams are performed and interpreted for many reasons and findings unrelated to pulmonary nodules, it is important that the radiologist is not distracted from other important findings.

Even when performed for high risk patients, chest X-rays and chest CT exams should always be fully evaluated for findings unrelated to lung cancer.

A study by Berbaum showed the effect of CAD on satisfaction of search in chest X-ray using 57 cases and 16 readers and found that CAD prompts, even those that always point to their target lesions without false positive error, fail to counteract satisfaction of search in a chest X-ray.

Also, CAD prompts may induce less visual search for abnormalities unrelated to the findings CAD is designed to detect. Similar results were reported by Krupinski.

Here I am going to give issues specific to chest X-ray and CT CAD. Ground truth definition is crucial for standalone and reader performance testing.

Ground truth identifies whether or not the patient has a chest abnormality, including lung and other organs or structures, whether or not the patient has pulmonary nodules, whether or not the patient has one or more cancerous pulmonary nodules. Ground truth identifies also precise location and extent of each nodule, as well as nodule description.

Pathology is necessary to determine the nodule type. However, not all pulmonary nodules undergo

a biopsy procedure. Alternatives for determination of the nodule type may include use of a panel of experts, PET/CT examination, and follow-up CT.

Ground truth for the nodule location and extent is determined usually by a panel of experts, and as shown here, there is great variations when outlining the border of the nodule how to take into account this variability in a ground truth and in locale assessment.

Here are the standalone performance testing. Just to remind you that the standalone performance measures are derived by comparing the location of a CAD mark to the location determined by the expert panel and by determining if the CAD mark sufficiently overlaps the ground truth. Note that standalone performance testing can be done using a larger database than used for reader performance testing.

The results of standalone performance testing for lung or chest CAD are highly dependent on nodule size, nodule location, CT protocols or type of X-ray acquisition technique, as well as co-morbidities affecting chest imaging.

The overall standalone performance measures

include sensitivity and number of false positives per scan on a lesion based and patient based analysis. It can be supplemented by a plot of the full FROC curve, if applicable.

Stratified standalone performance measures are also critical and a crucial competence, as it provides an understanding of the benefits and the drawbacks of CAD systems. Stratified measures may include nodule type, nodule characteristics, X-ray acquisition technique or CT protocols, co-morbidities affecting chest imaging.

We are going to talk about the reader performance testing issues. Remember that the majority of chest examinations are indicated for patients with symptoms unrelated to lung nodules.

Therefore, if a device is intended for use on a general population, the testing would need to encompass a full interpretation of all imaging findings. That is, the reader would then provide an assessment for pulmonary nodule detection as well as other diseases that are present.

If accounting for all uses of chest

examination and all possible chest diseases, such testing will simulate a so called "field test" where a field test is a real time, real life clinical assessment of a system.

Following the least burdensome approach, a retrospective reader study may replace field testing with the advantages of having multiple readers review all cases. However, such testing may not reflect the real time, real life clinical assessment of the CAD device, and bias may thus be introduced in such testing. How to limit or control such bias?

One of the things that is crucial also to look at for testing CAD is the reading paradigms. Chest CAD may fit in radiology work flow if implemented either as a second reader or as a concurrent reader.

An advantage of concurrent reader CAD over second reader CAD is that it may lead to a reduction in the reading time, especially for interpretation of the CT scan.

In fact, Kobayashi showed in one of his studies that the reader detection accuracy increases for both second reader and concurrent reader paradigms when

using a chest X-ray CAD.

Therefore, it may be necessary that the testing encompass all reading paradigms because one of the reading paradigms may be more practical and acceptable to the user and thus better respond to the user needs. Also, chest CAD indicated for use -- only for use as a second reader may not be adequately controlled at the software level.

Another competence that is crucial to talk about is the testing database, and here, for a general population indications for use for a chest CAD an enriched testing database may contain a majority of cases with no nodules and other chest diseases, enriched with cases having nodules varying in number, size, and morphology.

For a specific intended use of a chest CAD, an enriched testing database would account for few cases with no nodules, enriched with cases having pulmonary metastases and cases with low number of nodules of various size and morphology.

A stress testing database may include a majority of very difficult cases including smaller

nodules, nodules located in the hilum and central lungs, nodules located adjacent to blood vessels, nodules that are partially solid or have non-solid.

The study endpoints -- there are various possible endpoints depending on the general versus specific indications for use of CAD device and can be performed on a lesion based and patient based analysis. The corresponding assessment was presented in the "General CAD Methods" and "Statistical Issues" sections.

When identifying the study endpoints for either general versus specific indications for use, how critical is it to account for reader accuracy in other chest disease, reader location accuracy, number of detections made by the reader, whether or not all true nodules are detected by the reader, whether or not at least one of the true nodules is detected by the reader?

Also when looking for -- When identifying the study endpoints, it is important to remember that the clinical actions following both chest X-ray and chest CT may relate to many chest diseases. Therefore, how critical is it to capture the effect of a CAD designed to detect only nodules on the detection and diagnosis of

other disease?

Also, the clinical actions following both chest X-ray and chest CT is location specific. How critical is it to account for location accuracy?

I am finished with my talk. Thank you.

CHAIRMAN GLASSMAN: Thank you. Are there any questions for Dr. Paquerault? Dr. Berry, did you have a question? Yes.

DR. BERRY: In your slide 66 -- 36, you talk about false positives and, as I think you intimated, the issue of X-ray and CT in lung cancer screening is controversial, to say the least. I mean, it's the Hatfields and the McCoys.

My reading is that the evidence is not there that lung cancer screening prolongs survival. So I think it is paramount -- you may have heard me say that I didn't think that in colon cancer screening that the false positive issue was as important as in mammographic screening.

In lung cancer, in view of the circumstances, I think it is critical. So are you suggesting on that slide that CAD, in fact, increases the

false positive rate or are you suggesting that it is possible with CAD to, in fact, lower the false positive rate, which would be an enormous service?

DR. PAQUERAULT: Depending on the reader -- reading paradigm. If you use it as a second reader, you may highly increase your false positive.

DR. BERRY: Is it possible to arrange it so that you don't increase the false positive rate or, in fact, that you decrease --

DR. PAQUERAULT: Might be true.

DR. BERRY: I mean it would be a great service to increase the specificity of CT.

DR. PAQUERAULT: Yes, might be possible depending on your testing.

DR. BERRY: Sorry?

DR. PAQUERAULT: Depending on your testing and the standalone of the device as well. It needs to be tested by the reader. It might be possible.

DR. BERRY: Okay, thanks.

CHAIRMAN GLASSMAN: Any other questions? Yes, Dr. Tourassi?

DR. TOURASSI: I have a question about the

reading paradigms. In that slide, you state chest CAD indicate -- 52 -- Chest CAD indicated for use as a second reader may not be adequately controlled at the software level. What do you mean by that?

DR. PAQUERAULT: Well, you don't control the user, and there is no control on the software. So it is difficult. The software doesn't have controls to ensure that the device is going to be used as a second reader. If it is, the indications for use -- all right?

CHAIRMAN GLASSMAN: One more question.

DR. STEIER: Again, back to the false positive question which is very significant. In terms -- on the slides, you said the radiologists miss 50 percent, presumably some of which or many of which can be picked up by CAD.

Would CAD be picking up large, significant nodules, more than 8 millimeters, or are we talking about all sizes, including less than four millimeters, which would not be significant?

DR. PAQUERAULT: We were talking about chest X-ray in that slide, if I remember.

DR. STEIER: Yes.

DR. PAQUERAULT: Yes, and you don't see very little -- CAD may pick up very small nodules, but it is up to you to also say, yes, it's a nodule when you look at it.

DR. STEIER: Okay. So that 50 percent -- that includes nodules which may not be significant.

CHAIRMAN GLASSMAN: Yes.

DR. SAHINER: One question on your slide number 48, you said that if the device is intended for use in a general population for reader study design, the testing would need to encompass a full interpretation of all image findings.

So does that imply that, when the ground truth is also established, you would need to establish it for all kinds of lung abnormalities?

DR. PAQUERAULT: That's correct.

CHAIRMAN GLASSMAN: I just have one comment. I want to thank you very much for the presentation.

There was mention of PET/CT later on in the presentation, but not in the original management slide. I don't remember the number where nodules over 8 millimeters go to surgery and in usual clinical practice

in many places, a negative PET in a nodule over 8 millimeters would preclude surgery.

So that surgery is not the only management option at that point which I think may be important for us when we talk about the false positive issue because a lung biopsy is not a breast biopsy or a colonoscopy. That, of course, is one of the issues here.

Thank you.

DR. PAQUERAULT: Thank you.

CHAIRMAN GLASSMAN: We are now going to take a slightly earlier, or late, depending on whether you are looking at the agenda or your watch, 15 minute coffee and bathroom break. Thank you. Come back at 10:30, please.

(Whereupon, the foregoing matter went off the record at 10:15 a.m. and went back on the record at 10:31 a.m.)

CHAIRMAN GLASSMAN: We are now going to proceed with the first of two Open Public Hearing sessions for today's meeting. The second Open Public Hearing session will follow the FDA presentation on future issues with CAD this afternoon.

Ms. Wersto will now read a statement

prepared for the Open Public Hearings.

MS. WERSTO: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with a sponsor, their products and, if known, any of their direct competitors.

For example, this financial information may include a sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any financial relationships. If you choose not to address this issue of financial

relationships at the beginning of your statement, it will not preclude you from speaking. Thank you.

CHAIRMAN GLASSMAN: I would like to remind public observers at this meeting that, while this portion of the meeting is open to public observation, public attendees may not participate except at the specific request of the Chair.

I would ask at this time that persons addressing the Panel come forward to the microphone, and speak clearly as the transcriptionist is dependent on this means for providing an accurate transcription of the proceedings.

Please provide an electronic copy of your talk to the Executive Secretary for use by the transcriptionist to help to provide an accurate record of the proceedings.

Prior to the meeting, we received formal requests to speak during today's Open Public Hearing sessions. We are going to have two speakers who have asked in advance to speak.

I would also encourage anyone who would like to speak to the issue of current clinical uses for lung

CAD to have an opportunity at this time after these two speakers to come to the podium if you have any comments to make.

The first speaker is Dr. Eric Silfen from Philips Research of North America. Oh, and each speaker will have five minutes.

DR. SILFEN: I would like to thank the Advisory Panel for allowing me to make a few remarks. My name is Eric Silfen. I am the Senior Director for Biomedical Informatics Research for Philips Research North America.

My comments relate to my perceptions and notes that I have taken from this morning and yesterday's meeting.

So specifically, I just wanted to put out there what CAD systems are, and I want to reiterate that what we are developing are tools for clinical decision making. This is very, very important to understand.

It is tools that help physicians, and like tools they have certain indications for use, and they have indications for which they should not be used, and we have to be very, very clear as we develop these

decision-making tools what those indications are and what those indications should not be.

I want to discuss what I perceive as two concepts and one challenge in doing all of this. The key behind using computer assisted imaging is for radiologists, physicians who need to use the large amounts of image data that are generated on a daily basis, to be able to improve patient well-being.

We cannot afford to make decisions in the fashion shown here. We cannot deliberate. We cannot have secret collaborations. We cannot afford to do this in a very slow time frame. We cannot afford two years.

The information overload that is occurring in biomedicine right now is going to create significant pressures on us, and we have to be able to respond.

So the first concept: There was a lot of discussion about standalone evaluations and reader performance evaluations. The key issue for me is that the standalone evaluations are to create expert systems.

How can we have a computer assisted system that meets the performance criteria of an expert? For me as a practicing physician, and practicing emergency

medicine, I need something that could at least be as smart as I was and, hopefully, as smart as the consultant I would need to call upon to help me take care of a patient.

So that is the key behind developing the standalone evaluation protocol. The reader performance evaluation, to my mind, talks about how you are going to take this expert system and use it in clinical contexts.

These are very, very different uses; very, very different ways of developing the research protocols to establish whether or not a computer aided imaging system is valuable.

The second concept relates directly to this context of use. The systems can either help the expert be more expert under certain conditions, and the performance characteristics of the computer aided imaging system need to reflect that; or the system can be used for screening or diagnosis which are different.

The performance characteristics, the negative predictive values of these systems as we create them vary, depending upon their field of use. It is very important to understand this difference.

The third is the challenge, and the challenge is very, very significant. I will start off just by posing this question. It's a simple question.

When I was in medical school at Georgetown, I took a course taught by David Regalmann called "Studying a Study and Testing a Test," to teach physicians how to use statistics. So this question comes up all the time. What is sensitivity of a test?

Is it this or is it this? Not a trivial question to ask. The answer is the lower right. But if you were to go out and talk with physicians in practice on a daily basis who are not immersed in what we are doing and what we are talking about today and what we talked about yesterday, I feel that you would not get as clear a distinction, and that this understanding would not be present.

It is very important to understand these concepts going forward if physicians are to correctly use any type of computer assisted application in medical decision making.

CHAIRMAN GLASSMAN: Dr. Silfen, I am sorry, your five minutes is up.

DR. SILFEN: That's fine. The summary slide tells it all.

CHAIRMAN GLASSMAN: I'm sorry; your five minutes are up.

DR. SILFEN: That's fine. Thank you very much.

CHAIRMAN GLASSMAN: Thank you. Our next speaker is Mr. Joe Gardill from Healthcare Reimbursement RX, Inc.

MR. GARDILL: Thank you. I would like to make several points.

First, there is a study that exists that compares CTC, CAD, second read, the concurrent reader in the Biomedical Imaging and Intervention Journal 2007, Volume 3, titled "CTC: Investigation of the Optimal Reader Paradigm Using CAD," Taylor, et al.

Secondly, mammography CAD is appropriate as a second reader paradigm given that the gold standard for mammography is double reading. However, the FDA, is not considering cost and economics, only looking at safety and efficacy.

These are still important issues in the

adoption of these technologies in the clinical practices and communities, and I believe it is important for the Panel to give consideration of the impact of CAD use protocols on the adoption of these technologies.

As a second reader device, mammography CAD was valued by the AMA and CMS to reflect the incremental value and expense involved, and this resulted in a rapid adoption of the technology as an assistive device. However, CAD as an assistive device for CT and/or MRI is less appealing to practitioners as a second reader primarily due to the time element involved. Four views in a typical mammogram, hundreds of slices in a typical CT. However, reimbursement does play a role.

The valuation necessary to drive adoption as a second reader device would be seen as an economic burden to the health system payers and, similarly, the recent developments with 3D virtualization being "valued and/or bundled" into the underlying procedures would probably follow in this fashion as well.

Without a review by RUC, this actually devalues the procedure and would lead to widespread off-label usage as a concurrent reader without necessarily

evaluating the technology for this usage through the FDA process.

Should these devices be labeled as concurrent readers, the use would match the regulatory approval. Physicians would increase both efficiency and analysis over single reads, and a reasonable incremental valuation could be provided by the coding authorities which would further spur adoption. All of these results would qualify as least burdensome.

The challenge for the FDA is then to develop the appropriate scientific and statistical analyses to measure the incremental benefits provided by CAD during a concurrent review. I am confident that the vendors and the FDA can collectively achieve these goals and be least burdensome. Thank you.

CHAIRMAN GLASSMAN: Thank you very much. Is there anyone else here in the room who would like to speak to lung CAD at this time? Yes, sir? Please come forward and identify yourself.

DR. GUPTA: Hi. I am Alok Gupta from Siemens Healthcare. I wanted to provide a clarification on Dr. Paquerault's slide number 36 to which the Panel

had also brought attention on the number of false positives.

I just wanted to comment that the lung CT CAD devices are today mature enough that, although on some of the patients' exams false positives may go up to 10 or so, the vast majority of patient exams have very few false positives and, in fact, the PMA studies that we conducted from Siemens showed average of around two false positives and median about the same number.

So it is an important clarification, since that was a question from the Panel. Thank you.

CHAIRMAN GLASSMAN: Thank you very much. Do any of the Panel members have any questions for our three speakers -- Oh, one second. Anyone else want to speak? I'm sorry. Yes, sir.

DR. CLARK: Larry Clark from NCI. I work with Dr. Carl Jaffe. I oversee the branch of Technology Development for the Cancer Imaging Program.

I just want to make a comment and a request for the Panel to perhaps take another look at a slightly different area that might be advantageous for the issue of standalone evaluation.

For the last five years, we have been involved in the development of a database to evaluate lung cancer screening methodologies. The point I want to make is it took five years to develop a consensus on those methods, and also there is various technology limitations that took a longer time for that to evolve.

The question I am posing to this panel is if there was a consensus formed for a database as a reference database where the scientists that NCI would engage and engage the FDA and our colleagues at NIST -- if there was a consensus on this design, on the case enrichment, on the method of annotation, which is actually quite complex, is there a sense on this Panel that a reference database of that kind could be recognized as maybe a first process of an approval of CAD tools and, more importantly, CAD tools which goes through various upgrades in terms of performance that would be a cost effective way of performing the relative valuation of those tools?

CHAIRMAN GLASSMAN: Thank you very much. Yes, in the back, please.

DR. NAIDICH: Good afternoon. My name is

David Naidich. I am a radiologist, a professor of radiology at NYU. My field of interest is chest. I was the PI for the Siemens multi-center clinical trial that was presented to the FDA for PMA approval for their CAD product, and I am a paid consultant for them.

Just one observation: I think one distinction that should be made between CAD for mammography and CAD for colon and CAD for lung, from a purely logical and conventional sense for how CT particulars are read - - Most cases don't require CAD.

So that the notion that you would use this technology for every case is something I think you need to take into consideration.

For example, if you have someone who has 25 nodules in their lung from metastatic disease, I don't need CAD to find the 26th; or similarly, if you have a 23-year-old who is being evaluated on CT because of potential bronchiectasis or a whole host of infectious problems, having a CAD would, frankly, be of very little value to you.

So that I think, when you take into consideration how you would use this in the paradigm for

how you would interact with it, as a sequential read or as a concurrent read, you really don't want a situation where every single time the CT comes up, you are forced to, in fact, look at marks that may have virtually no relevance to the clinical scenario in which you are operating and which could, in fact, delay or, in fact, obscure your spending time looking at other pertinent findings.

CHAIRMAN GLASSMAN: Thank you. Does anyone else want to come to the microphone? If not, do any of the Panel members have any questions for any of the speakers?

DR. CARRINO: I have a question for Dr. Naidich. So to summarize your feeling then, it would be that for pulmonary CAD, all you would need is a second reader paradigm and not a concurrent use?

DR. NAIDICH: I think, if by concurrent every single time you were to, in fact, look at a CT scan, you have marks that were not relevant to what you were trying to do, and there are a substantial number of cases that would, in fact, come under that heading, then why would you want to have an automatic force to read

things that you don't need to look at.

DR. CARRINO: Right, and I would also say that you are -- you would say this should be tested on a population where there is a higher prevalence for the disease of interest, looking for pulmonary nodules, lung cancer?

DR. NAIDICH: Well, I think it is going to be individualized radiologists, radiologist clinical scenario to clinical scenario. But clearly, to detect nodules, I would think from a clinical standpoint would be optimally directed toward either those cases for which you suspect it might be a nodule and you don't see one or for which finding additional nodules may, in fact, be of value. But weigh that against the kind of case where, for example, someone comes with unresectable lung cancer with direct invasion of the mediastinum and adrenal disease, finding a 3 millimeter nodule in the contralateral lung doesn't really have much significance.

Really, the cases -- the majority of cases that we actually look at clinically frequently fall into that category.

DR. CARRINO: Thank you.