UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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RADIOLOGICAL DEVICES PANEL

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October 24, 2012
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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M E E T I N G

(8:09 a.m.)

DR. ROSENBERG: Good morning, everybody.

I'd like to call this meeting of the Radiological Devices Panel to order. It is now 8:09 a.m.

I am Dr. Robert Rosenberg, Chairperson of the Panel. I'm a diagnostic radiologist specializing in mammography, from Albuquerque, New Mexico, Radiologic Associates of Albuquerque.

And now I would like to let the rest of the Panel introduce themselves. We might as well go counterclockwise, starting with Ms. Morris.

MS. MORRIS: Good morning. Janine Morris. I'm the Division Director for the Division of Radiological Health [sic] in CDRH.

DR. SIMON: Good morning. Dr. Dan Simon. I'm Medical Director of Vascular Access Center of West Orange in lovely West Orange, New Jersey.

DR. WATSON: I'm Karol Watson, Director of Preventive Cardiology at UCLA, and cardiac imaging.

DR. FAULK: Good morning. Robert Faulk, private practice, specialty in breast imaging.

DR. J. SMITH: Good morning. I'm Dr. Justin Smith. I'm a radiologist in Bellevue, Washington, and I'm President of the Washington State Radiological Society. My interest is in machine learning and computer-

aided diagnostic imaging.

DR. KRUPINSKI: Elizabeth Krupinski. I'm Professor and Vice Chair of Research and Education in the Department of Medical Imaging at the University of Arizona, and I'm an experimental psychologist with expertise in medical image perception, observer performance, image quality assessment, and human factors.

DR. PAYNE: Tom Payne. And I'm a medical physicist. I specialize in testing mammary units and CT units, and I'm a private consultant.

MS. CRAIG: Shanika Craig. I'm the DFO for this meeting.

DR. COLDWELL: Good morning. I'm Doug Coldwell. I'm an interventional radiologist and Professor of Radiology at the University of Louisville in, actually, beautiful Kentucky.

DR. ZISKIN: I'm Marvin Ziskin. I'm a Professor of Radiology and Medical Physics at Temple University in Philadelphia, and I'm the Director of its Center for Biomedical Physics.

DR. DODD: I'm Lori Dodd. I'm a biostatistician at the National Institute of Allergy and Infectious Diseases. Prior to being at NIAID, I was at the National Cancer Institute for seven years, working with the cancer imaging program.

DR. HOOLEY: My name is Dr. Regina Hooley, and I'm an assistant professor and a breast imager at Yale University.

MS. GEORGE: I'm Elisabeth George. I'm the Vice President of Global Regulations and Standards at Philips Healthcare, and I'm here as the Industry Representative.

DR. VEGA: Good morning. Buenos dias. My name is Dr. Marlena Vega. I'm a three-time cancer survivor, fourth generation. I am a psycho-oncologist, and I am the E.D. of A Will to Live/Sobrevivir, a breast cancer organization.

MS. PRICE: I'm Carol Price, and I'm a breast cancer survivor, a registered nurse, and I'm the Consumer Representative through the Komen organization.

DR. ROSENBERG: Okay, I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on a premarket approval application supplement (P080003/S001) to expand the indications for use of the Selenia Dimensions 3D System with C-View Software Module, sponsored by Hologic, Inc.

The Selenia Dimensions 3D System is currently approved (PMA Number P080003) for breast cancer screening and diagnosis. The screening examination can consist of full-field digital mammography alone or a combination of full-field digital mammography with digital breast

tomosynthesis.

The new C-View software module can generate synthesized 2D images from the digital breast tomographic data. Hologic would like to expand the indications for use to allow the combination of digital breast tomosynthesis with synthesized 2D images to be used as another exam option for breast cancer screening.

And I'd like to also thank the distinguished members of the Panel for their time and interest.

Okay, if you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Shanika Craig, the Designated Federal Officer for the Radiological Devices Panel, will make some introductory comments.

MS. CRAIG: Good morning. I will now read the Conflict of Interest and Deputization to Temporary Voting Member Statements.

The FDA Conflict of Interest Disclosure Statement, a particular matter involving specific parties, Radiological Devices Panel of the Medical Devices Advisory Committee, October 24th, 2012.

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 (FACA) of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular

Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of the Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found in U.S. Code 18 Section 208 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 the Federal ethics and conflict of interest laws. Under U.S. Code 18 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.

Related to the discussion 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 U.S. Code 18 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.

For today's agenda, the Panel will discuss, make recommendations, and vote on the premarket approval application

supplement to expand the indications for the use of the Selenia Dimensions 3D System that is currently approved for breast cancer screening and diagnosis.

The screening examination can consist of full-field digital mammography alone or the combination of FFDM with digital breast tomosynthesis. The new C-View Software Module can generate synthetic 2D images from the DBT data. Hologic requests to expand the indications for use to allow the combination of DBT with synthetic 2D images to be used as another exam option for breast cancer screening.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with U.S. Code 18 Section 208. A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

Elisabeth M. George is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Philips Healthcare.

We would like to remind members and consultants that if the discussion involves 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 participants to

advise the Panel of any financial relationships that they may have with any firm at issue.

Appointment to temporary voting status.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August 18th, 2006, I appoint the following individuals as voting members of the Radiological Devices Panel for the duration of this meeting on October 24th, 2012:

Dr. Robert M. Faulk, Dr. Marvin C. Ziskin, Dr. Karol E. Watson, Dr. Elizabeth A. Krupinski, Dr. Regina J. Hooley, Dr. Daniel W. Simon, and Dr. Justin P. Smith.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the materials to be considered today's meeting.

This has been signed by Dr. Jeffrey Shuren, Director of Center for Devices and Radiological Health, on October 16th, 2012.

For the duration of the Radiological Devices Panel meeting on October 24th, 2012, Marlena Vega has been appointed to serve as a temporary non-voting member. For the record, Dr. Vega serves as a consultant and patient representative to the Oncologic Drugs Advisory Committee at the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of

interest review and has reviewed the material to be considered at this meeting.

This appointment was authorized by Jill Hartzler Warner, Acting Associate Commissioner for Special Medical Programs, on October 17th, 2012.

Before I turn the meeting back over to Dr. Rosenberg, I'd like to make a few general announcements.

Just a reminder that the entirety of today's meeting will be recorded by an official transcriptionist, and the official transcript will be made available on the FDA website. The transcript for today's meeting is also available through Free State Court Reporting, and their phone number is (410) 974-0947. Information for purchasing videos of today's meeting can be found on the table outside the meeting room.

The press contact for today's meeting is Michelle Bolek. She's in the back, waving her hand.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has been concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with Mr. James Clark at the registration

desk.

In order to help the transcriber keep in order everyone who is speaking, please be sure that you identify yourself each and every time that you speak, and turn your microphone on to speak and off when you're done.

Thank you very much.

Dr. Rosenberg.

DR. ROSENBERG: And silence your cell phones.

Okay, we are ahead of schedule. We will now proceed to the Sponsor presentation.

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

Please, Hologic.

DR. SOLTANI: Good morning. My name is Peter Soltani. I'm the Senior VP and General Manager for Hologic's Breast Health business team. I am a full-time employee of the company.

First, I'd like to thank the Panel for your time today.

Before we start the clinical presentation, I'd like to take a moment to share with you what's happened with tomo since PMA approval about 18 months ago.

So as of this moment, there are over 300 clinical institutions in the U.S., in 46 states plus Puerto Rico, that have adopted tomo. The clinical

feedback has thus far exceeded everyone's expectations. Sites report significant reductions in the callback rates or false positives, while simultaneously observing dramatic improvements in cancer detection rates. I can personally tell you that not a week goes by that I don't hear about a patient whose cancer was missed with 2D and only picked up with tomosynthesis. So everyone's quite pleased with the clinical outcomes.

Today, though, we're here to present the next step in the evolution of tomo. It's the Selenia Dimensions C-View Software Module. This application is designed to take the tomo data and synthesize the 2D image for the radiologist to use as a roadmap to guide the review of the tomo image dataset. And that's in the absence of a conventional 2D mammogram.

And presenting to you today will be Dr. Andy Smith, who heads our image science team; Dr. Loren Niklason, who's head of our tomosynthesis programs at Hologic; Dr. Rafferty, who heads the Avon Breast Center at Mass. General Hospital. Dr. Rafferty, of course, was the PI on the tomo study and has been gracious enough to continue in that vein as the PI of the current study.

In addition to the presenters, we have a team available to answer any questions that may arise. They include Dr. Stein, our Chief Technology Officer, Dr. Jing, our Chief Science Officer, Mr. Arthur Friedman, our Senior VP of Regulatory Affairs, and also Dr. Halpern from Mass General and also a colleague of Dr. Rafferty.

And with that, I would like to turn it over to Dr. Smith.

DR. A. SMITH: Good morning, everyone. My name is Andy Smith. I'm Vice President of Imaging Science for Hologic, and I am a full-time employee of Hologic. I'm going to give you an overview of the technology and how it works.

I'd like to just start with some nomenclature that we'll be using throughout the presentation, so it's quite clear what we mean.

When we refer to 2D FFDM, that refers to conventional digital mammography.

When we refer to 3D, that's tomosynthesis. We use those two terms interchangeably.

2D plus 3D and combo refer to when there's a 2D digital mammogram and the tomosynthesis images are acquired together, and that is the currently approved screening indication that uses tomosynthesis.

When we talk about C-View or synthesized 2D, that refers to a projectional 2D image that's calculated from the 3D dataset. And this, of course, does not require additional radiation exposure. It's calculated from the original tomosynthesis scan.

And 3Ds and 3D plus C-View represent the same thing and is the additional optional mode that we're seeking approval for. And the way this works, only tomosynthesis images are acquired and then we synthesize the 2D image. These two images together are read. And this is the proposed

new screening optional indication for use that we're seeking approval.

This is just a picture of the Dimensions 2D/3D system that's currently approved.

So in terms of the currently approved modes, this is the tomosynthesis mode, and the way it works is we perform a 3D imaging, which generates projection images, which are then reconstructed into the tomosynthesis slices. There's also a 2D image, a conventional 2D FFDM acquired, and then the review is the 3D and 2D together.

So this is the currently approved combo mode, and we had previously presented two methods of using this. One was a full two-view, where there'd be a two-view 2D and a two-view 3D CC and MLO. And we also presented data on an MLO-only view, where there'd be two-view 2D and a single-view 3D MLO. And then, of course, there's also the 2D mode, which is approved for screening.

The proposed additional optional mode, 3D plus C-View, looks quite similar in a flowchart form. We perform the 3D imaging as we currently do and reconstruct. That's unchanged. What is changed is we no longer acquire a 2D image. We synthesize the 2D image, called C-View, and then the 3D and the C-View image are reviewed together.

So how does it work? Well, the tomosynthesis scan works in the standard way with our existing product. The tube moves over a 15-degree arc and takes 15 exposures, and then you take those projection

images and reconstruct them into the tomosynthesis slices.

Just to remind you, those are reconstructed at 1 mm thickness, so you'll get approximately 60 of those slices.

Both the scan and the reconstruction that we're proposing in the new mode will be exactly the same as the current product. What we do now is we synthesize the 2D image, the C-View image, and that algorithm is quite similar to a maximum intensity projection, or MIP, that's commonly done with MRI images.

So this is just one image example. Dr. Rafferty will show you lots of clinical examples. On the left, we have a conventional 2D FFDM image, and on the right, a synthesized 2D image from the 3D dataset. I'm just putting this up here to show that they look quite similar, which I think is not unexpected because they both represent images created from the X-ray attenuation through the breast.

How is it used? As I mentioned, the C-View is part of the 3D dataset. And the image is identified. It was not identified in the previous slide to avoid any possible confusion with true 2D FFDM images.

And this just shows the examples. On the right, there's a little mark which is burned into the image, and that's how we identify it.

So what are the system changes that we're seeking approval for? Well, this synthesized 2D algorithm is a software module, and as I mentioned, the mode of operation for screening, the 3D plus C-View, would

be an option which will be still available along with all the existing 2D and 2D plus 3D modes. So we're not removing any of the existing modes. We're just seeking approval for an additional option using the C-View.

And in terms of the intended use, we're seeking for this mode the same uses as we have, which is for the use in screening and diagnostic mammography.

The current intended use statement says that the screening examination will consist of either a 2D image set or a 2D and 3D image set, and now we're adding this proposed new use, which would be a 3D image set in combination with the synthesized 2D image.

So with that, I would like to turn the presentation over to Dr. Rafferty.

DR. RAFFERTY: Thank you.

Good morning. My name is Betty Rafferty. I'm the Director of Breast Imaging at Mass General in Boston, and I was the principal investigator for this clinical trial, and I paid my own expenses to be here today.

Mammography works. Annual mammography has shown the ability to reduce the mortality rate from breast cancer anywhere from 15% to 50%. But having said that, we all know that mammography is not perfect. As many as 20% of breast cancers will be missed on a mammogram.

Additionally, about 10% of women are recalled for additional workup from screening, and a significant proportion of them actually have no

abnormality, resulting in unnecessary anxiety and cost.

A major factor contributing to this limited performance of mammography is the tissue superimposition that is created by the overlap of normal breast structures in a two-dimensional projectional image. These overlapping structures can result in two effects.

They can obscure a lesion, making it more difficult to perceive. In this digital MLO mammogram we see a subtle asymmetry here, but it's impossible to further classify it.

Conversely, by mimicking mammographic lesions, overlapping structures can generate false positive findings at screening, resulting in unnecessary recalls.

In this example, an asymmetry in the subareolar region of the CC view, again, is recalled from screening because it requires additional evaluation.

Now, given that tomosynthesis can minimize the impact of overlapping structures in the breast, we would anticipate that it has certain benefits. First, increased breast cancer detection. Next, decreased recall rate for non-cancer cases, improved margin visibility, and then, because it's a 3D study, more precise lesion localization.

So if we look at our example of the MLO view with the asymmetry, we see here a view of the 2D example.

Looking at our tomosynthesis dataset side by side, we can page

through the breast at 1 mm intervals, and now we can see that actually this asymmetry is really a spiculated mass, and this was an invasive ductal carcinoma.

If we look at our second example, the asymmetry in the subareolar region, similarly we can page through the breast at 1 mm intervals, looking at the structures in the subareolar region. And in evaluating for summation, we can generally pick out the individual normal structures, which are widely separated in space, but which summate to create the asymmetry that we see on the two-dimensional projection image.

Now, combined digital mammography and breast tomosynthesis were approved for clinical use by the FDA in February of 2011.

These are the ROC curves from the two reader studies that we presented as part of that 2D plus 3D PMA submission. And here you can see the performance of the radiologists regarding two-dimensional FFDM compared to their superior performance when they used the combination of 2D plus 3D imaging.

And we've realized that the benefits of tomo have even exceeded our expectations. In about a month, in Chicago, at the Radiological Society of North America, nine abstracts will be presented detailing the positive benefits of 2D plus 3D for both screening and diagnostic applications in the clinical environment.

But while evidence of the clinical benefits of 3D are accruing,

attention has also been drawn to the incremental increase in dose over 2D FFDM. In this histogram, we can see the dose for 2D FFDM on the left compared with the dose for the combination imaging, 2D plus 3D, on the right.

Now, while it's important to realize that all of these imaging modes are below the FDA MQSA dose limit of 3 mGy, the imaging community is always striving to minimize dose while maintaining quality.

One strategy for reducing dose is to perform only the 3D MLO in addition to the 2D FFDM. In the prior histogram, we can see that that will result in an intermediate level of dose.

We presented data for this imaging mode during our 2D plus 3D PMA submission. And here you can see that the combination of 2D FFDM plus the 3D MLO was actually statistically significantly better in performance than 2D FFDM alone, but it realized only about half of the incremental gain that was attained when we used 2D FFDM plus two-view tomosynthesis.

So that brings us to the rationale for 3D plus C-View. Realizing the advantage of two-view tomosynthesis, that suggests an alternative strategy to reduce dose while capitalizing on the benefits of 3D, namely the elimination of the 2D mammogram.

Now, having said that, in interpreting the 3D study, there is certainly value to the radiologist in having a two-dimensional summary image available. First, it can help in the assessment of side-to-side symmetry.

Here's an example of standard 2D FFDM mammogram CC views.

And here are the corresponding C views generated from the tomosynthesis dataset.

Here are the MLO 2D FFDM views for that same patient.

And here are the C-View MLO views generated, again, from the 3D dataset.

We can also use the summary image in assessing for interval change.

Here we are sitting at the workstation. We're looking at our current examination on the bottom and our prior examinations on the top using 2D FFDM.

But we can also use C-View in the same way, and here we can see an example of that workflow.

Now, the aesthetic of the C-View image may be a little different, but this is a common situation encountered in clinical practice. It's certainly one that we have to face when comparing digital mammography with prior analog imaging, and it's one that we also face comparing digital mammography with prior imaging from a different digital vendor or with prior imaging using different processing algorithms. In fact, this situation presents itself whenever technology changes, and radiologists have always been able to meet that challenge in clinical practice.

Another situation where a summary image may be useful is in the detection of calcifications, and I'd like to show you some examples.

In the first example, we have some linear calcifications on the 2D FFDM image. And here's a blown-up image for your benefit. Here you can see the linear calcifications on the 2D FFDM view.

Here on the C-View image we're going to look at the same area, and here's that area electronically zoomed for you, again, from the C-View.

So we have the 2D FFDM on the left and the C-View image in the middle. If we look at the 3D slices themselves, you can see that the actual calcifications are not all visible on the same slice. You actually have to go through several slices in order to be able to see them. And so there's clearly value in the C-View image being able to depict the totality of the calcifications in one projectional image.

In the next case we're looking at amorphous calcifications on the MLO and CC views of this 2D FFDM image on the left, and the same calcifications on the C-View MLO and CC images in the middle, and the individual slices from the 3D dataset are on the right, again, MLO and CC projections, and you can see that they look quite similar.

In the third example, we're going to look at a very faint tiny cluster of calcifications. On the left is the 2D FFDM image. In this lighting you can barely see the calcifications right here. The C-View image is in the

middle, and again we can make out that tiny cluster of calcifications. On the right is a single image from the 3D dataset, again showing this tiny cluster of calcifications, which we hope we see during our clinical day.

In Case 4, we're looking at a cluster of calcifications here on a 2D FFDM image. In the center, again, we see a cluster of calcifications using the C-View imaging. And on the right, we're going to go through the tomosynthesis dataset, and as we page through in 1 mm increments, we cannot only confirm that we see those calcifications, but now we can appreciate that they're associated with a spiculated mass because we've removed the impact of the overlapping structures. And this is a major benefit of the tomosynthesis, being able to unmask an unsuspected finding on the mammogram, which signals more significant disease here, invasive and in situ ductal carcinoma.

The last benefit of a summary image is the recognition of the distributional aspect of particular features, especially calcifications.

Here, if we look on this example, there are segmental calcifications in the subareolar region of the right breast. We can see them here on the zoomed-in image.

Here on the C-View we can look at the same area and again see those calcifications.

If I have the 2D on the left and the C-View in the center, we can now look at our tomosynthesis imaging and see that the most lateral

calcifications come into view initially. And then, as I proceed more superiorly in the breast, those calcifications actually fade away, and I can now see the more medial aspect of the calcifications. So you can see that the distributional nature of these calcifications are actually better depicted on the two-dimensional projection than the actual cross-sectional images.

So 3D plus C-View imaging provides another low-dose tomosynthesis imaging option for the radiologist. And our study was designed to compare the diagnostic accuracy of 3D plus C-View to the current standard 2D FFDM.

Now let's look at the clinical study overview.

Cases were accrued from 22 sites under IRB approval, and the subjects presented for either screening or biopsy. They underwent investigational 2D and 3D imaging in a single compression of both breasts in the MLO and CC views. The screening subjects also underwent standard of care 2D FFDM imaging on the same day. Biopsy subjects were eligible for the study if their standard of care imaging had been performed within the past 60 days. The standard of care imaging and the investigational imaging were interpreted by different radiologists at the accruing sites.

Now, certain subjects were excluded from the study based on clinical criteria. First, they were women who had presented with a prior excisional biopsy. A prior surgical biopsy often leaves architectural distortion on a mammogram.

When a reader in a reader study is presented with such a finding in the absence of appropriate clinical data and correlative imaging, they'll of necessity come to the conclusion that that represents a worrisome finding and call that patient back, resulting in excessive false positives. In the appropriate clinical setting, however, the radiologist with the correct clinical information and having the correlative imaging data would never come to that inappropriate conclusion.

Second, women with an internal breast marker. At biopsy, we often place a tissue-marking clip in the lesion being biopsied, and those lesions often turn out to be a cancer. We're going to present readers in a reader study with imaging, asking them to find a cancer, so we wouldn't already want to have pre-marked that cancer with a clip.

Women with breast implants and breasts that are too large to be imaged in a single compression represent a situation where these women would have to undergo more than the eight investigational images in order to have their entire breast covered with the imaging process. And we thought that that degree of radiation was excessive in the investigational setting.

So these women were excluded based on clinical criteria. But having said that, the C-View algorithm works perfectly well in these situations, and I'd like to show you some examples.

First, here's a woman who's had a prior benign excisional biopsy on her breast, and we can see some subtle architectural distortion

here, displayed on the C-View image.

This next woman has multiple surgical clips and postoperative change here in her excisional bed and her prior treatment for lumpectomy, and we can see that the algorithm performed well on this image.

This is a woman who's had a prior lumpectomy, and we can see a breast implant in the non-displaced view on this particular image.

In the next image, a different woman has a displaced view of her implant now. We can also see some segmental pleomorphic calcifications on this C-View image, signifying extensive DCIS.

This is an example of a breast that is too large to fit on the 24 x 30 detector in a single compression. And yet, although the entire breast is not covered on the detector, the algorithm performs well.

The eligible collected cases were then classified into one of four categories, biopsy proven malignant cases, biopsy proven benign cases, cases recalled from screening, based either on the reading of the standard of care or investigational imaging, and cases that were classified as negative, based on a negative interpretation of both the standard of care and investigational imaging. So essentially a double red negative. The reference standard for malignant cases was pathology, and for the non-malignant cases, one-year follow-up to confirm their non-malignant status.

This is a flow chart showing you that a number of women were also excluded from inclusion in the study set based on QC criteria. In fact,

590 subjects were excluded at QC. And this seems like a very large number. But what we have to realize is that the entire case had to be excluded if any one of the eight images acquired failed to pass QC. The acquisition protocol did not allow the technologists to repeat any of the imaging in the investigational phase.

Now, the quality control exclusions were things similar to what we see in clinical imaging. The majority were patient motion, but there was also positioning exclusions, gridlines, artifacts, et cetera. In fact, in total, only approximately 3% of the images were excluded, and this is very similar to what we see in clinical practice.

In my practice at MGH, 2.6% of the images are rejected in a repeat analysis. The number of 2D and 3D exclusions were approximately equal. In fact, the number of 2D exclusions was greater than the number of 3D exclusions.

So if we look at this number, of 19.8%, in terms of the subjects, we can see that this is really generated by the fact that the entire case had to be excluded if any one of these eight images failed to pass QC.

Having said that, when reviewing the cases for similarities in the included and excluded cases, they were very similar in terms of age, breast density, and ethnicity.

Now let's look at an overview of the reader study.

This was a comparison of 3D plus C-View to 2D FFDM. It was a

retrospective, enriched reader study involving 302 cases reviewed by 15 radiologists. The radiologists were MQSA qualified and had a varying range of experience in both 2D and 3D interpretation.

The primary endpoint of the study was that the area under the curve for 3D plus C-View imaging would be non-inferior to that of 2D FFDM.

There were also two secondary endpoints. The area under the curve for subjects with dense breast tissue using 3D plus C-View would be non-inferior to that of 2D FFDM, and the non-cancer recall rate for 3D plus C-View would be non-inferior to that of 2D FFDM.

We tried to make the reader study cohort, as much as possible, reflect clinical practice. And here you can see that we wanted the proportion of calcification features and non-calcification features to be similar to what we saw in the clinical environment. And you can see here, for cases that contained features, about 30% of them were calcifications and about 70% of them were non-calcifications.

If we take those 176 cases and add the 126 negatives, we get the 302 cases included in the cohort.

Similarly, we wanted the cases to reflect an approximate 50/50 mix in terms of dense and fatty parenchymal patterns. Here on the pie chart we can see that the blue and green represent fatty parenchymal patterns, BI-RADS Density 1 and 2, and the yellow and the red reflect dense parenchymal patterns, BI-RADS Category 3 and 4.

Now, the vast majority of the cancers included in the reader study came from the biopsy cohort -- 73 of the 77, in fact -- and had already been diagnosed by conventional methods prior to enrollment. This method of case selection actually biases the study against demonstrating a gain in sensitivity using 3D plus C-View because nearly all of the cancers had already been detected with 2D FFDM imaging. So sensitivity was not an endpoint of the study, given the case selection bias.

Now, as I had said, 15 readers participated in the study, and they had a varying degree of mammography reading experience. There were high-volume readers interpreting more than 5,000 mammograms a year, medium-volume readers interpreting between 3,000 and 5,000 mammograms a year, and low-volume readers interpreting 3,000 mammograms a year or less. Additionally, all the readers were asked whether they had had prior clinical experience in interpreting tomosynthesis imaging.

This table demonstrates the reader experience. We can see that four of the readers were low-volume mammographic readers, six of the readers were medium-volume readers, and five of the readers were high-volume readers. Approximately half of the readers in the reader study had had prior clinical experience using tomosynthesis and half had not.

Now, regardless of the fact of whether the reader had had prior experience or not, using the tomosynthesis imaging, they all were trained prior to initiation of the reader study, and the training focused on the

interpretation of the 3D dataset because that's really the heart of this imaging modality. We looked at both normal anatomy, the appropriate resolution of summation artifact, and then the appearance of mammographic features.

C-View images were presented with each training case that was reviewed, and emphasis was placed on the use of the C-View image to function as an overview or summary to guide interpretation of the 3D dataset in a way similar to using a MIP to help in the interpretation of a breast MRI.

The readers read two assessment sets, and performance thresholds were measured for Assessment Set 2. In total, the readers reviewed approximately 150 cases for training purposes, and none of the training cases were used in the reader study itself.

This schematic gives you an idea of the reader study construction. In the first session, readers read 302 cases, half FFDM and half 3D plus C-View. Then, after a one-month washout period, the readers returned and again read 302 cases, half 3D plus C-View, half 2D FFDM, and then the data analysis was conducted.

Scoring was lesion-based, and only actionable lesions were marked. Up to three lesions could be marked per case. The lesion location and type were recorded for each lesion to confirm that the reader really had seen the cancer in the case.

The scoring proceeded by initially recording the case as a

BI-RADS 0, indicating that it needed to be recalled for evaluation, or a BI-RADS 1 or 2. If the reader scored it as a BI-RADS 0, they were then asked to provide a forced BI-RADS score of between 1 and 5, indicating their best guess as to what the case would turn out to be. And for all cases, a probability of malignancy ranging from 0% to 100% was obtained for each case.

And now I'm going to ask Dr. Niklason to discuss the data analysis.

DR. NIKLASON: Thank you, Dr. Rafferty.

I'm Loren Niklason. I'm Director of Tomosynthesis Programs and a full-time employee of Hologic. I'd like to talk about the data analysis and the study design.

As Dr. Rafferty mentioned, the primary endpoint of this study was non-inferiority of the area under the curve for 3Ds versus 2D FFDM, and the study was designed as a non-inferiority study because the radiation dose and other risks were equivalent or very similar.

We used a delta of 5% to define non-inferiority. The probability of malignancy scores were used for the ROC analysis, and the highest score assigned to any lesion in a case was applied to that case for the ROC analysis. We used a p-value of less than .05 to define significant difference, and this was prospectively defined.

And, finally, this retrospective, enriched ROC study design is

similar to the previous approval for a 2D FFDM study -- a 2D FFDM plus 3D study and previous 2D FFDM systems.

We had two secondary endpoints. The first was area under the curve for subjects with dense breasts. It was non-inferior to that of 2D FFDM for 3Ds. Again, a delta of 5%, and the probability of malignancy scores were used for the analysis.

And the final endpoint was the non-cancer recall rate. For 3Ds, it is non-inferior to that of 2D FFDM. We used, again, a delta of 5%, and all the non-cancer cases were included in this analysis. And we used the initial BI-RADS score for this analysis, in which the radiologist was asked to provide either a 0 for a recall or a 1 or 2 for a non-recall.

The analysis of the recall rate was performed using a bootstrapping analysis for individuals and for all readers. And this analysis allows determination of confidence intervals based on randomly selecting new samples of readers and cases from the original sample.

Next, I'd like to talk a little bit about the ROC curves and the analysis.

An ROC curve is a plot of the true positive fraction on the vertical axis, or the sensitivity, and the false positive fraction or one minus the specificity on the horizontal axis. In breast imaging, this could also be referred to as the non-cancer recall rate.

The better a system is, the closer it is to this upper left-hand

corner. A perfect system would have 100% sensitivity and 100% specificity, so it would be right up in this corner. And as technology would improve or get better, it would move towards that corner of the graph.

The benefit of using ROC analysis is that we can plot a radiologist's performance over a range of decision thresholds. And for example, if they move to a higher recall rate, they will have a higher cancer detection; a lower recall rate, a lower cancer detection.

And the ROC curve is the standard method for measuring two systems at this stage of development.

In comparing two systems with ROC analysis, again, as I mentioned in the previous graph, the one closest to the upper left-hand corner, in this case the yellow curve, is the superior or the better device. And to measure that difference in this study, we'll use the area under the curve as a metric for diagnostic accuracy, and the difference in the areas under the curve is what we'll report for the incremental benefit of System 2 versus System 1.

Finally, when you have two systems, each with an ROC curve, the radiologist can use the benefit of the improved system in several ways. They can improve their sensitivity, for example, in this case, keeping their recall rate at 10% and using the entire benefit to improve cancer detection, or they can move along the horizontal direction and reduce the recall rate, while their sensitivity is maintained, or some combination of the two.

I'd like to turn it back over to Dr. Rafferty to present the reader study results.

DR. RAFFERTY: Thank you.

Predetermined thresholds for reader performance had been set for both 2D and 3D imaging. Application of those predetermined thresholds resulted in several of the radiologists not meeting criteria for inclusion in the data analysis, predominantly based on their interpretation of the 2D FFDM images. After discussion with the FDA, it was decided to include all 15 readers in the data analysis. But subsequent analyses confirmed nearly identical outcomes, regardless of the thresholding standards applied.

In terms of the primary endpoint, the AUC difference for 3D plus C-View imaging being non-inferior to that of 2D FFDM.

This chart actually shows the AUC data for all readers, across all cases. And we can see that the mean difference in the area under the curve for 3D plus C-View versus 2D FFDM was .040. The lower limit of the confidence interval of the area under the curve was greater than the delta of -.05, proving non-inferiority. And, in fact, that was greater than zero, proving superiority at a p-value of .005. In fact, 14 of the 15 readers actually displayed an increase in the area under the curve for 3D plus C-View versus their 2D FFDM performance.

This is a graphical depiction of the ROC curve, with the white line being the radiologists' performance reading 2D FFDM and the yellow line

being their performance reading 3D plus C-View. You can see that the difference in the area under the curve is .040, being significant at a p-value of .005.

So in terms of the primary endpoint using multi-reader/multi-case ROC analysis, 3D plus C-View imaging was non-inferior to 2D FFDM and was, in fact, superior to 2D FFDM. Fourteen out of the 15 radiologists demonstrated improvement in the area under the curve with 3D plus C-View compared to 2D FFDM.

In this clinical example, I'll draw your attention to the superior aspect of the breast here on this 2D FFDM image. Here it is electronically zoomed for you.

If we look at the corresponding area on the C-View image, we can electronically zoom that, as well.

Reading the 2D FFDM, 6 out of the 15 readers recalled this case for further evaluation, yielding a mean POM score of 8.5%.

Using 3D plus C-View, as we page through the tomosynthesis dataset, we can see that there's actually a large spiculated mass here, an invasive lobular carcinoma. If we recall that on the 2D exam, 6 out of the 15 readers recalled this case. Using 3D plus C-View, all 15 of the readers recalled this case for further evaluation. And the mean probability of malignancy increased from 8.5% on 2D FFDM to 91.3% using 3D plus C-View.

So the primary endpoint was met.

In terms of the secondary endpoint, looking at the performance in dense breast tissue, these are the ROC AUC values for all readers, across dense breast cases.

And we can see here that the mean difference in ROC AUC for the readers using 3D plus C-View versus 2D FFDM was .045. Again, the lower limit of the confidence interval for the AUC difference was greater than the delta of -.05, proving non-inferiority, and the p-value was .027. Again, 14 out of the 15 readers demonstrated improvement in the area under the curve using 3D plus C-View versus 2D FFDM.

Here we can see a graphical depiction of the ROC analyses showing the change in the area under the curve at .045, with a resultant p-value of .027.

So for the secondary endpoint involving dense breast tissue using multi-reader/multi-case ROC analysis, 3D plus C-View imaging was non-inferior to 2D FFDM, and 14 out of the 15 radiologists demonstrated improvement in the area under the curve using 3D plus C-View compared to 2D FFDM.

Here's a clinical example from the trial. Looking at the standard 2D mammogram, I'll draw your attention to a very subtle asymmetry on the MLO view. I'll electronically zoom that for you.

We'll look at the same image on the patient's C-View and again electronically zoom that.

On the 2D imaging, 4 out of the 15 readers recalled this for additional evaluation, yielding a mean probability of malignancy of 14.4%.

If we now look at the 3D plus C-View and page through the tomosynthesis dataset, we can see that there's actually a small spiculated mass here, a tubular cancer. If you recall, on the 2D imaging dataset, 4 out of the 15 readers recalled the case. But using 3D plus C-View, 10 of the 15 readers recalled the case, and the mean probability of malignancy score went from 14.4% on the 2D FFDM imaging to 46.1% using 3D plus C-View.

So the secondary endpoint for dense breast tissue was met.

Looking at the secondary endpoint for non-cancer recall rate, here we see a table showing the non-cancer cases and the recall rates of the 15 readers. Now, the non-cancer cases comprised cases which had been recalled at the accruing sites; negatives and histologically proven benign cases, 225 in total.

Looking at the mean performance for the radiologists reading the 2D FFDM, on average they recalled 103 of the negative cases using 2D FFDM and recalled 72 of the cases using 3D plus C-View. This resulted in a relative reduction in the recall rate of 30%. In fact, every single radiologist had a statistically significant reduction in their recall rate using 3D plus C-View compared to their performance using 2D FFDM.

If we now look at a smaller case set comprising just the cases which had been recalled at the accruing site and their negatives, something a

little more akin to a screening population, a total of 150 cases, here we see that on average, using 2D FFDM, the readers recalled 53 cases. Using 3D plus C-View, on average they recalled 31 cases, resulting in a relative reduction in their recall rate of 41%.

So in terms of the secondary endpoint for non-cancer recall rate using bootstrapping analysis, this secondary endpoint was met and 3D plus C-View was non-inferior to 2D FFDM. In fact, it was superior to 2D FFDM. And every radiologist had a statistically significant reduction in their non-cancer recall rate using 3D plus C-View.

In this example from the clinical trial, looking at the CC view, there's an asymmetry out here laterally, which I'll electronically zoom. This looks worrisome to me. I would recall this in my clinical practice.

Looking at the same area on the C-View, here we can see that, again, it looks worrisome.

Using the 2D FFDM, 11 of the 15 readers recalled this case for additional evaluation.

Now, using the 3D plus C-View, we can use the C-View as our summary image and then let that guide us in our evaluation of the 3D dataset. And as we page through, we can see that, in fact, there's no occult mass, just normal parenchymal fascial elements, Cooper's ligaments. This is a nice illustration of using tomosynthesis to evaluate for summation artifact, which this case was. If you recall that on the 2D imaging, 11 of the 15 readers

recalled this case. Using 3D plus C-View, only 2 of the 15 readers recalled this case.

So the secondary endpoint for non-cancer recall rate was met.

So a summary of the endpoints.

The primary endpoint was met, and the 3D plus C-View was shown to be superior to 2D FFDM for the primary endpoint: diagnostic accuracy for all cases.

The secondary endpoints were also met, and that 3D plus C-View was shown to be non-inferior to 2D FFDM for diagnostic accuracy in dense breast tissue and shown to be superior to 2D FFDM for non-cancer recall rate.

Now let's look at risk/benefit analysis.

As I said earlier, clinical trials have demonstrated that screening mammography reduces breast cancer mortality by anywhere from 15% to 50%. And these numbers are conservative, and many people think that the benefit is actually larger.

In this recent study that was published, looking at the longitudinal analysis of the European screening trials, we see that the likely mortality reduction, even when accounting for overtreatment, is at least 30% to 50%. So, clearly, screening represents a benefit.

We can use the BEIR VII analysis to estimate lifetime mortality risk from annual mammography from the ages of 40 to 80. And doing that

risk analysis for 2D FFDM shows that the attributable risk is .00020, a very tiny number. And for 3D plus C-View it is .00024, a very similar tiny number.

This histogram shows the dosing data for currently available digital mammographic imaging. On the left is the 2D FFDM Hologic Dimensions image. Second from the left is the average 2D FFDM dosing across the United States, according to the 2005 MQSA data. The two bars on the right represent the currently approved imaging modes for tomosynthesis, the 2D plus C-View combo imaging on the right and the 2D plus MLO-only tomosynthesis second from the right.

So the proposed new imaging option of 3D plus C-View would represent an additional tomosynthesis imaging mode that would allow two-view tomosynthesis imaging at a dose similar to FFDM.

Now, in our prior PMA submission, we demonstrated that the currently available modes of tomosynthesis imaging had superior accuracy, based on the areas under the curve, compared to 2D FFDM. And in the current application, we've seen that the 3D plus C-View proposed mode also has superior diagnostic accuracy when compared to FFDM at a dose that is lower than either of the currently available tomosynthesis imaging modes.

Let's look at some additional analyses. First, calcification versus non-calcification cases.

On the left are the ROC curves for the readers looking at non-calcification cases, and you can see that there is a change in the area

under the curve of .045, in favor of 3D plus C-View, yielding a p-value of .011. In fact, 13 of the 15 readers improved their performance using 3D plus C-View imaging.

But now looking at the calcification cases, we can see here also that 3D plus C-View outperformed the 2D FFDM, with the difference in the area under the curve being .039 and yielding a p-value of .025. And 13 out of the 15 readers improved their performance for calcification cases using 3D plus C-View versus 2D FFDM.

Here's an example. In this cropped image we see a group of pleomorphic calcifications on 2D FFDM imaging. Thirteen out of 15 readers recalled this case for additional evaluation.

In the center we have the C-View image of this same area, and on the right, we can look at the tomosynthesis dataset that it's paired with. Here, as we scroll through, we can see the group of pleomorphic calcifications here. And in this case, 15 out of 15 readers recalled these calcifications for additional evaluation.

Looking now at the analysis for fatty breast tissue. We had previously looked at dense breast tissue as one of the secondary endpoints. Here you can see the ROC curves for patients having predominantly fatty breast tissue, and you can see that there was an increase in the area under the curve for 3D plus C-View versus 2D FFDM of .025, with a resultant p-value of .042. In fact, 13 out of 15 readers improved their performance in fatty

breast tissue using 3D plus C-View.

Here's an example at the workstation. This is a patient with parenchymal Pattern 1 fatty breast tissue, a standard 2D FFDM mammogram.

Here, at the workstation, we can see the corresponding C-View images. I'll draw your attention to an asymmetry in the right breast on the CC view.

Let's look at it first on the 2D images. Here it is electronically zoomed for you.

Here it is on the C-View images, also electronically zoomed.

So we have the 2D and the 2D imaging. Eight out of 15 readers recalled this case, with a mean probability of malignancy of 14.4%.

Here we have the 3D plus the C-View. If we go through our 3D imaging dataset, we can see that this is actually a spiculated mass. And recall that 8 out of 15 readers recalled this on 2D, but 13 out of the 15 readers recalled this on 3D, and the probability of malignancy increased from 14.4% on the 2D imaging to 60.1% on the 3D imaging.

Let's quickly look at a cancer recall analysis.

Looking at the recall rates for the 77 cancers for all 15 readers, we see that on average, looking at the 2D FFDM recalls, the readers recalled 63.4% -- I'm sorry -- 63.4 of the cancers. Using the 3D plus C-View, on average they recalled 65.7 of the 77 cancers. So here we see that the readers were able to maintain their cancer detection rate, while experiencing a

significant reduction in their recall rate.

Last, let's look at the distribution of cases.

The FDA questioned the impact of case mix on the outcome of the study. The 3D plus C-View study does have more negative cases and more cancer cases than our prior 2D plus 3D PMA submission.

Here you can see a pie graph from the two submissions. On the top, the 2D plus 3D PMA had been enriched with the number of recall cases, as you can see here. The current 3D plus C-View submission is enriched with the number of negative cases to more closely reflect clinical practice.

Analyses were done to determine if the results of the study would change as a function of case distribution, and a number of permutations were evaluated, including a permutation of cancers plus benign-proven lesions plus recalls, which was more similar in case mix to the 2D plus 3D PMA.

Here we can see the results of those analyses for different case distributions, and we can see that, regardless of the case distribution, the areas under the curve for the difference between 3D plus C-View and 2D FFDM was approximately .040. And all of the case distributions yielded a statistically significant result. So the result of the trial was unchanged, regardless of the case mix.

So, in summary, all primary and secondary endpoints were met or exceeded. 3D plus C-View is a two-view tomosynthesis imaging option that

is superior to 2D FFDM at a comparable dose.

And I'll show you one final case. Here on this MLO image, I'll direct your attention to the center of the breast and electronically zoom that for you.

Let's look at the comparable area on the C-View image, again electronically zoomed.

On the 2D imaging, 5 of the 15 readers recalled this -- and I'd say good for them -- with a mean probability of malignancy of 4.9%.

If we now look at the 3D plus the C-View and we page through the tomosynthesis imaging dataset, we can see that there's actually an irregular spiculated mass here. This was an invasive mucinous carcinoma. If you recall, on the 2D imaging dataset, 5 of the 15 readers had recalled this. Using 3D plus C-View, every reader recalled the case, and the mean probability of malignancy went from 4.9% using 2D FFDM to 94.9% using 3D plus C-View.

So, in conclusion, the data from our reader study has demonstrated that 3D plus C-View is effective for clinical use. The analysis of benefits and risk for 3D plus C-View support that it is safe for clinical use. And 3D plus C-View provides a lower-dose, two-view option for tomosynthesis imaging that will help radiologists reduce their recall rate and find cancers, translating to reduced patient anxiety and lives saved.

And I thank you for your attention.

DR. ROSENBERG: Okay, thank you very much. I'd like to thank the Sponsor's representatives for their presentation.

Does anyone on the Panel have a brief clarifying question for the Sponsor? Please remember that the Panel may also ask the Sponsor questions during the Panel deliberations in the afternoon.

And, again, start with your name. You can just start. Let's just kind of start around. Anybody have questions?

DR. FAULK: Dr. Faulk.

One question I'm a little bit confused about, and maybe you could expound upon. In the study design, I'm a little bit confused about the role of C-View in detection versus diagnosis and DBT. So I think I read through that, and if I remember correctly, it said that the radiologists were instructed not to use C-View for diagnosis but only DBT.

But does that mean that they couldn't use C-View for detection? And if so, were there cases where they detected it on C-View but not DBT?

DR. RAFFERTY: So that's a good question. So, basically, the C-View cannot exist unless the 3D dataset exists because the C-View is created from the 3D dataset. So the readers were instructed that they should not use the C-View in isolation to make a decision. Clearly, the C-View is going to function as a summary image to guide the radiologist as they then approach the 3D dataset. What we would not want is for the radiologist to

look at the C-View and disregard the 3D dataset.

So the radiologist might see a feature, for example, calcifications, as I showed you several examples of on the C-View image. But then they would use the 3D dataset not only to confirm that there were calcifications, but also to confirm that they were associated with one another, because calcifications can appear to be grouped on a projectional image when they are, in fact, separated in space. So you'd want to confirm what your assessment is of the summary image using the 3D dataset.

Additionally, the 3D dataset can give you independent information. For example, unmasking a mask that you might not have seen otherwise, demonstrating multi-focal or multi-centric disease, things of that nature.

So the radiologists were instructed that they should not use the C-View in isolation, that it was to be used in combination with the 3D dataset, but then you would make your judgment based on that combination of imaging.

DR. FAULK: So just to clarify that. Then the final assessment of the POM was not determined just by DBT alone?

DR. RAFFERTY: The final assessment was the combined C-View plus 3D.

DR. KRUPINSKI: Elizabeth Krupinski.

Just to follow up on that one, I guess. In the actual clinical

practice, would there be a statement coming with the system that says, you know, sort of like CAD, you must view the C-View first and you must view the DBT in order to get the best diagnoses?

And then I guess part of that also is that part of the hanging protocol. Does it come always kind of like how you were showing, with the C-View on one side and then the DBT, the tomosynthesis on the other side, always up together, kind of forcing the person to read both at the same time, or is it a sequential presentation? Or is there an option?

DR. RAFFERTY: I think that, you know, I'm not sort of a mandater-type person, but I think that most radiologists look at that 2D projectional image to try and get their bearings in terms of looking at the 3D dataset. And while I think you could certainly try either, I've not known anyone to look at these images who did not approach it in that mode, to look at the C-View first, get your overview, and then look at the 3D dataset, not letting the C-View bias you against the 3D dataset, because you have to look at the images carefully and clearly. And as you point out, the hanging protocol can be adjusted to facilitate your doing that.

DR. PAYNE: Well, I'm a medical physicist, so I can't resist. Everything so far was very clean.

DR. RAFFERTY: Oh, no, I feel like running.

DR. PAYNE: You might as well go sit down.

DR. RAFFERTY: We have physicists here. I can go sit.

DR. PAYNE: I know.

DR. RAFFERTY: Would you like one of our physicists?

DR. PAYNE: I beg the question, in terms of -- and you have responded to this, but just to open it up. You know, the synthesized 2D images will not be identical to a full-field digital. By that I'm referring to differences in spatial resolution, some low contrast detectability, the definition of detection of fibril spec groups, masses. In other words, as we know, this is linear tomography. Okay, pure and simple. It's pure, but it's not simple, okay, in terms of there are obviously very good and very elaborate reconstruction algorithms that are used to come up with the synthesized C-View.

But I think, just to make sure we know what we're doing, at least my clinical colleagues, in a physics world, the images are not quite as good. And by that I mean the specs. I would anticipate the specs probably won't be degraded by very much. Masses certainly not by very much. But the fibrils, the linear structures, it depends on whether they're perpendicular to the motion or parallel to the motion. So there's a little degradation in that sense.

And then the other difference is going to be the time it takes to acquire. In the tomosynthesis, I think that's typically about a four-second acquisition --

DR. RAFFERTY: That is correct.

DR. PAYNE: -- versus a standard acquisition of a standard -- of a full-field digital, which for one view is usually less than a second. Somewhere around a second. So there's a time difference for acquisition and then there's some blurring aspects.

So maybe just comment on that, that's all.

DR. RAFFERTY: So I will just actually invite one of my physicist colleagues up here to make sure that they can answer your question more completely.

I'll just say, from a clinical perspective, the imaging really looks quite comparable in terms of allowing me to use that summary image for the things that I need to do clinically. But I want to ask one of my colleagues to respond to your specific questions about image parameters.

DR. A. SMITH: Hi, my name is Andy Smith.

You're right that the characteristics are not completely identical for the synthesized 2D to our conventional 2D system. But the resolution characteristics are quite good. We reconstruct to around 100 μ, a quite similar resolution to currently available FFDM systems.

And, of course, the real benefit of 3D imaging is the elimination of superimposed parenchyma, something that's not really well characterized or measured using these standard phantoms since you don't -- you know, just looking at the C-View sort of by itself doesn't tell you very much about the imaging performance of the system as a whole, in terms of the 3D plus

C-View.

And I do think that the clinical trials sort of stand for themselves. The fact that we were able to demonstrate a superior performance using C-View plus 3D compared to 2D alone, you know, for the detection of both masses and calcifications sort of indicates that, in fact, this combined system does perform adequately clinically. And I'm not sure that I can comment on anything more than that, other than really the clinical results speak for themselves.

And there is a large-scale prospective screening trial which is taking place in Oslo in Norway, which Dr. Rafferty can talk about, where they are using the C-View algorithm routinely in clinical use, and the performance of that has been quite significantly better than conventional digital mammography.

DR. ROSENBERG: A quick question. Because these are synthesized images, those resolutions you've talked about, you're going from a 75 μ pixel size on initial image, and you're reconstructing it at 100.

Is that homogenous performance across the thickness of the breast? Are there any issues with differences in that contrast or spatial resolution on the reconstructed images?

DR. A. SMITH: No, the reconstructed images are isotropic, independent of breast type.

DR. ROSENBERG: And then the other question is, I think, for

Dr. Rafferty. Yeah, I'm not sure you can answer. There was some difference in performance between the C-View images that you presented --

DR. RAFFERTY: Um-hum.

DR. ROSENBERG: -- and the presentation -- I guess it was almost two years ago -- of 3D with standard full field mammography that had improved performance.

Do you have any comments on the difference?

DR. RAFFERTY: Well, this particular application involved obviously different cases and different readers, and we didn't compare 3D plus C-View against the combination imaging.

Having said that, as Dr. Smith alluded to, Per Skaane and his group in Oslo, Norway are about to complete a two-year accrual of a large screening trial that will comprise 25,000 women using various permutations of 3D imaging. So the arms are standard 2D FFDM, 2D plus CAD, 2D plus 3D, the combination imaging, and 3D plus C-View. And he presented his preliminary results at RSNA last year, demonstrating that 3D plus C-View performed almost identically to combination imaging in clinical practice

And the other significant thing about that trial is that he was using the C-View image to function in just the way I described, as the summary image, using that as an initial overview and using it to compare to prior imaging. And I can say that, since that initial presentation, Dr. Skaane has indicated and told me that the results are even more promising, and he

completely believes that 3D plus C-View is the way that he will go in the future.

And, certainly, for those of you who might not be familiar with Dr. Skaane, he basically oversaw two of the foundational trials in digital mammography, Oslo I and Oslo II, right after the beginning of digital mammography. So he's always been interested in digital mammography in a screening population.

So I think that that study, because it's in a clinical setting using real patients, all these permutations, very difficult to do in the United States, is going to have a tremendous impact on how we practice.

DR. KRUPINSKI: Can I follow up? Just out of curiosity, how did it do compared to the 2D with CAD, which has the lower dose? So is 3D --

DR. RAFFERTY: Um-hum.

DR. KRUPINSKI: -- outperforming 2D with CAD?

DR. RAFFERTY: It is. And I can actually, yeah, put up a slide to actually kind of show you.

DR. A. SMITH: Slide 9 of the backup.

DR. RAFFERTY: Oh, does someone handle that remotely? Wow. My instinct is to just go on the laptop and find it myself.

MR. NIKLASON: I can do it.

DR. RAFFERTY: Yeah. Don't we have to do that?

DR. A. SMITH: The three of us together can solve this.

DR. RAFFERTY: Yes.

MR. NIKLASON: Now just click on here, and then hit nine.

DR. RAFFERTY: Nice, okay. So this was actually Dr. Skaane's presentation at RSNA last year, just the title slide from it, showing him and his group. But this is a summary of his interim results.

So here you can see that using 2D, the cancer detection rate -- 2D alone, the cancer detection rate was 57%, 2D plus CAD, 60%, 2D plus 3D, the standard combination imaging, 83% and 3D plus C-View, 77%. And, again, all of these occurred in the clinical setting and for the 3D plus C-View, using the 3D plus C-View to compare independently to the priors.

Now, these are low numbers. They were just his interim results, but he indicates that the results get even better for C-View. And the accrual will end in December.

DR. ZISKIN: I have a couple of questions. The first one --

DR. ROSENBERG: This is Dr. Ziskin.

DR. ZISKIN: What's that?

DR. ROSENBERG: I'm just putting your name in, Dr. Ziskin.

DR. ZISKIN: Oh, I'm Marvin Ziskin, Temple University.

In the case study that you talked about, if I understand it correctly, about 50% of the cases were abnormal with cancer. And what I wanted to know was have you had an experience with a mix that would be closer to clinical practice than the 50%, and how the 3D plus the C-View

would do on that?

DR. RAFFERTY: Again, the dataset was enriched because this was a clinical trial looking for regulatory approval, and that was the least burdensome way to approach this rather than doing it in a real screening environment, where the incidence of breast cancer is so low and it would obviously take so long to complete.

So we did evaluate the cases that we have, using various case distributions, to see whether the case distribution mix would affect the outcome. And it did not, as I showed.

But probably the closest thing to what you're talking to is really what Dr. Skaane's data is going to be, true performance in the clinical setting, which we're not going to be able to do here in the United States before, hopefully, 3D plus C-View gets approval.

DR. ZISKIN: Thank you. Another question has to do with one of the exclusions in the sample set had to do with a prior incisional biopsy.

DR. RAFFERTY: Yes.

DR. ZISKIN: And I wanted to get a little better feel for that.

DR. RAFFERTY: Um-hum.

DR. ZISKIN: First of all, roughly what percentage of cases in clinical practice would this constitute?

DR. RAFFERTY: Well, it's actually interesting. There's not that much data on this, although the paper people most often quote is a paper of

Dr. Sickles, showing that after a benign excisional biopsy, only about 3% of women will show lasting mammographic change.

I have to say that using combination imaging in my practice, a benign excisional biopsy will far more often result in change that's visible on the 3D dataset because of the removal of superimposed structures allowing you to see more subtle architectural distortion.

And so the reason those women were excluded is that the reader, being faced with that image, now sees subtle architectural distortion, particularly if it's only on, say, the 3D dataset and they assume that that's worrisome, because that's what you should do. But they don't have appropriate clinical context or any correlative or prior imaging, whereas sitting in the hospital, as I'm looking at that same case, I can see that that woman had a benign excisional biopsy two years ago. I actually might have the images from the needle localization. I will never make that mistake in clinical practice that I will make as a reader in a reader study.

And so it just seems to me that that will unnecessarily result in false positives, diluting the true value of the technique in the setting of a reader study, even though in clinical practice that would not be problematic. And we've not found that to be problematic using combination imaging in clinical practice in the presence of appropriate clinical history and correlative imaging.

DR. ZISKIN: Thank you.

DR. RAFFERTY: Um-hum.

DR. DODD: Lori Dodd.

I have two questions. The first is that you stated that the biopsy cases represented the majority of the cancers and that the interval between the FFDM and the 3Ds could be up to 60 days. So I'm interested in knowing the distribution of the timing between those two scans.

Do you have any data on that, the timing between the FFDM and the 3Ds?

DR. RAFFERTY: For the biopsy cohort?

DR. DODD: Right.

DR. RAFFERTY: Well, it could be anywhere within 60 days, but I, myself, don't know any more about the distribution of that. The reason that that was done, let me just say, is that women undergoing a biopsy are extremely anxious, and it's then now an additional thing to ask them to participate in an investigational trial. Women are incredibly altruistic. They want to participate and help other women. But we didn't want to have them have to have yet more additional imaging being yet an additional burden.

But I'll ask if any of the rest of the panel knows. So I don't think that we know that answer for you. I can just say that in clinical practice, interestingly, many of our patients have 60 days elapse between their biopsy and their definitive surgery, whether they seek another opinion. We're a tertiary care facility, so that's not at all unusual for me to see that, and I don't

see any significant difference in their imaging, clinically, when they've been biopsied two months previously, usually at another institution.

DR. DODD: Okay. So I guess the question is whether there were any significant changes in the FFDM, which was the 2D image that was compared to the 3Ds in that 60-day interval. My understanding is that it was the 2D image that was the FFDM.

DR. RAFFERTY: Oh.

DR. DODD: And so the question is -- there was a statement made that, because these were cancers that were detected by FFDM, this would bias in terms of improved sensitivity for FFDM. But that might not be the case if there were subtle changes or even big changes that bias towards actually the later image showing features that were more indicative of cancer.

DR. RAFFERTY: So I'm hearing a couple of things in your question, so let me just say this part to make sure that I've been clear.

So the patients presenting, for example, from the screening cohort underwent the investigational imaging, which is essentially combo 2D plus 3D, eight images, four of them being standard FFDM, four of them being tomo, two images of each breast. Those women also then had another mammogram done, which would be their standard of care image, on the same day. The women in the biopsy cohort came, agreed to participate and had the eight images done, the combination imaging, and that was those

images. The 2D FFDM from that experience was what was used in the study.

So whether or not there was interval change from the patients' standard of care imaging, the point of that was that their standard of care imaging didn't have to be repeated for the biopsy cohort. Whether there was interval change, I don't know the answer to that except to say, clinically, that we don't see interval change in that scenario generally.

DR. DODD: Okay. So the comparisons of the 2D FFDM with the 3Ds were done on images --

DR. RAFFERTY: The same day.

DR. DODD: Okay. And then the other question has to do with the washout period. My understanding of the reader study is that there were two sessions. At the first session, the reader read half FFDM and half the 3Ds. And then, at the second session, which was a month later, they read the other half of each of the sets.

DR. RAFFERTY: Exactly.

DR. DODD: Were there any analyses looking at whether there was a tendency for the later -- the Session 2 scans to have an improved diagnostic accuracy, or was there any concern that the washout interval was not long enough?

DR. RAFFERTY: Was not long enough. I'll actually --

DR. NIKLASON: No, we didn't analyze that.

DR. RAFFERTY: Yeah, we didn't analyze that.

DR. DODD: Okay.

DR. RAFFERTY: Yeah.

DR. DODD: Thanks.

DR. HOOLEY: My name is Regina Hooley, and I have a couple of questions.

The images that you showed of the microcalcifications on the C-View were very impressive. However, I just want to clarify. In the study, was the sensitivity for all the calcification lesions equivalent for the 3D plus the C-View compared to the 2D FFDM?

DR. RAFFERTY: So we did not do a specific sensitivity analysis for calcification lesions versus non-calcification lesions. Basically, the sensitivity analyses that were done used the BI-RADS score, a 4 or a 5 being a positive or a 1, 2, or 3 being a negative, to look at overall performance of 3D plus C-View versus 2D FFDM, because in terms of the study design, it was not designed to show an increase in sensitivity for one imaging technique over the other. That's why we used ROC analysis.

So as you rightly point out, the ROC analysis for the calcifications was superior using 3D plus C-View compared to 2D FFDM.

DR. HOOLEY: Okay. And I just have another question and comment regarding the exclusion of women who had excisional biopsies. The women who have breast conservation and excisional biopsy, those scars are fairly obvious and very straightforward.

DR. RAFFERTY: Um-hum.

DR. HOOLEY: I think the women who have benign excisional biopsies, those scars can be quite subtle and often non-visible on the regular 2D mammogram.

DR. RAFFERTY: Agree.

DR. HOOLEY: And on the tomosynthesis views, these scars can actually be much more prominent.

DR. RAFFERTY: I would totally agree.

DR. HOOLEY: And with the combo view, since it's taken from the data acquisition of the tomo images, then I would believe that those scars would also be more prominent. And then, when you're comparing with the 2D prior mammogram, one might not even have appreciated that scar in the past and now see it and you can say, well, I know because, on my history sheet, the lady had -- this woman had a biopsy in this area.

But I still believe that it would be natural for the radiologist to want to call back that patient, in which case there will be a slightly higher recall rate. And, in fact, maybe the specificity might be falsely elevated in the study, although how often this happens, I don't know. You know, I don't know if anybody knows how often this would actually happen, where that post-benign biopsy excisional scar will be much more prominent to prompt to recall.

DR. RAFFERTY: I totally agree with your observation, and that

sort of echoes what I was trying to convey earlier, that the post-excisional change can be much more prominent on the 3D because you've unmasked it from the surrounding structures.

Having said that, we've been using the combination imaging for a year and a half, and basically we have not seen an elevation in the recall rate, again because I think we're fairly strict about looking at the images, trying to correlate with what the patient has already had.

I'm hearing what you're saying, but that's kind of a challenge that we're faced with every day. You can reposition another 2D mammogram and see subtle architectural distortion from prior surgical change. And, again, as the radiologist, you have to make some sort of judgment about that, using the information that's available to you. I'm not saying that it would never be a problem, but we have not found it to be a significant problem that precludes us or would deter us from using tomosynthesis in our practice.

DR. HOOLEY: Although my understanding is that, currently, now you still have the 2D FFDM images also as a comparative tool.

DR. RAFFERTY: That's true. But I think that the general principle holds true, that I always teach the fellows that you're as ugly as your ugliest view. And the fact that we would see some architectural distortion on that tomosynthesis image, even if the 2D image looked totally pristine, it would not deter me from trying to figure out what that image is. And it would also not comfort me more, necessarily, if I could not correlate that well

to a prior excisional site.

We have a couple of dramatic cases, that patients have had prior excisional biopsies and developed architectural distortion in another area of the breast that have turned out to be cancer. And, again, it underscores the need to do really careful correlation with the patient's prior history and any correlative imaging that you have.

DR. ZISKIN: Marvin Ziskin here.

I have a question about Reader Number 7.

(Laughter.)

DR. ZISKIN: Reader Number 7 did worse with the 3Ds system than the standard. I was wondering if you had any sort of insight into why that might be. Is it a matter of training or something else?

DR. RAFFERTY: I honestly don't know, and I don't personally know who Reader Number 7 is. I can say it's not me because I was not a reader. But I guess it's not unimaginable that, of the 15 people, one of them didn't get it, as they say.

I think that in clinical practice we see some people who may need some element of retraining. I think that this underscores the need to audit yourself in your own practice. That's a feature that we have emphasized in our clinical practice, how am I doing personally, is my recall rate going up instead of down, am I finding less cancers, not more, so that you can make the appropriate adjustments. And I think that Reader 7, in the

real world, is not necessarily unique.

DR. ZISKIN: Thank you.

DR. ROSENBERG: Please.

DR. VEGA: Hi. I have two observations. I'd like to piggyback on Regina because -- well, the one and only Marlena Vega, who has all of those scars.

I was wondering if any pursuit has been done, or information, regarding ethnic disparities, for some of us keloid and some of us heal on a very different level.

And the second piece is in terms of cultural diversity and sensitivity. I'm wondering how some communities view coming back and having the different kinds of it, because I think that it's hard enough to get some of the women that I deal with just in there and they say, I'm not going to press my breasts, and then to come back again and come back again and compare. So I wish you good luck with that because I know it's very difficult. Not unwarranted, but a difficult thing.

And I'm thinking -- I'm actually pleading while you're still here, asking people to take into account that many ethnic minorities have very different views of all of this and also have healing rates. So I guess it's a platform and a question.

DR. RAFFERTY: So, first, I want to thank you for those comments. They're very welcome.

I think, in terms of the relative performance between different ethnic groups, we're a little too early in the maturation of the technology to be able to speak to that. But it's my hope that not even just in specific ethnic subgroups, but that all women do not want to be called back if they don't have anything wrong with them. It's incredibly anxiety inducing and for many women becomes a barrier to ever coming again for screening. And so for people like me who believe strongly in screening, we want to do everything that we can to reduce the false positive rate.

To your point about the keloids. Using the 3D imaging, we're able to tell whether a specific lesion is in the skin or not. So the issue of keloiding does not become a clinical problem using the 3D technology.

The issue of differential healing would speak a little bit to what Dr. Hooley was mentioning previously. And I'm not quite sure where we are. It's going to be a very interesting thing to look at and something that we certainly observe in clinical practice.

DR. VEGA: Yeah, I know, because my scars have flattened over the period, along with my personality, but they really have flattened considerably and changed. And I've had a variety of different, you know, incisions, whatever.

DR. RAFFERTY: Um-hum.

DR. VEGA: And I thought about it and thought that in the beginning I was so worked up when we saw it. And then something that I

think is so wonderful that I would like to suggest, and that is the idea that you get across to people, not just the baseline, but that there's hope in some way for them to compare things and have control of some issues, because you feel so out of control psychologically when, in fact, you have any kind of diagnosis. So that's a very nice piece to say on your side, so to speak.

DR. RAFFERTY: I could not agree with you more.

DR. ROSENBERG: All right, Dr. Watson, and then we'll take a break.

DR. WATSON: It's Karol Watson, UCLA.

I just wanted to piggyback on Dr. Ziskin's comment. Reader Number 7 reminds me a lot of what happens in cardiac imaging. Every time we go to the next platform or the next level, you see the same thing. There are some readers who adopt it right away, and there are some readers who take a little time to get up to speed. So I think that it's not a reason not to move to the next level. But we see this very commonly in cardiac imaging.

DR. ROSENBERG: All right, it is now -- I have 9:48. We'll take a five-minute break and return for the FDA.

Thank you all.

DR. RAFFERTY: Thank you.

(Off the record.)

(On the record.)

DR. ROSENBERG: I would like to call this meeting back to order.

And the FDA will now begin their presentation.

Dr. Ochs.

DR. OCHS: Good morning. My name is Robert Ochs. Today I'll give a brief introduction and background, and then we'll discuss the clinical study design, the statistical results, and the clinical significance. And I'll provide some additional background information for the Panel discussion.

I'd also like to acknowledge members of the FDA review team who are from across the Center.

The Selenia Dimensions 3D System is currently approved for breast cancer screening and diagnosis. The screening exam can consist of full-field digital mammography alone or the combination of FFDM with digital breast tomosynthesis.

This submission is for a premarket approval or a supplement for the Selenia Dimensions 3D System with C-View Software Module. The software provides the ability to create synthesized 2D images from the 3D data. And I'll mention, there is no other significant hardware or software changes with this supplement. And Hologic would like to expand the indications for use of the system so that 3D plus synthesized 2D images can be used for screening.

And I'll note, in our presentation we use 3Ds to refer to the 3D plus synthesized 2D image set.

So the indications for use are essentially the same, and I've

highlighted in yellow what Hologic would like to expand. So Hologic would like to include a new option so that a 3D image set in combination with a synthesized 2D image set can be used for breast cancer screening.

Now, the C-View software module can generate the synthesized images from the 3D data, and this is similar to a maximum intensity production. And the images will include a C-View mark to alert users that they are not FFDM images.

A few additional notes on the configuration. The default contrast of the synthesized 2D images can be set to low, medium, or high, and the medium contrast was used for the reader study. The appearance of the skin line on the synthesized 2D images can be set to less or more prominent, and the more prominent skin line was used for the reader study. So these are both two user-configurable options of the C-View system.

Hologic's PMA supplement was reviewed in the context of the proposed indications for use and the potential impact on the clinical practice of mammography.

And for the Panel discussion, we'd like the Panel to consider the potential impact on performing mammography when using 3Ds and not acquiring FFDM images, potential study biases, study exclusions, and the safety, effectiveness, and benefit/risk of the new option.

I'd like to introduce the next speaker, Dr. Weijie Chen.

DR. CHEN: Good morning. My name is Weijie Chen. I'm a

scientist from the Division of Imaging and Applied Mathematics at CDRH. So I will talk about the clinical study design in this application.

I will first talk about the general considerations regarding controlled multi-reader/multi-case, or MRMC, study and the ROC methodology. Then I will talk about specific aspects in the pivotal study design in this application, including the objective of the study, the methods for case selection, the characteristics of readers, and the method for image interpretation. The materials in this presentation are mainly related to Panel Questions Number 2 and 3.

The key question to answer in this study is, is the Selenia Dimensions 3Ds non-inferior to the standard of care 2D FFDM for breast cancer screening and the methodology of the controlled multi-reader/multi-case study with ROC methodology?

Some general considerations regarding prospective versus controlled retrospective clinical studies.

In a prospective clinical study, the reader decisions affect patient management, and multiple readers usually do not read the same case. And there is typically no enrichment of cases. Reading conditions may be difficult to control in a real-world, multi-institutional situation. And it can lead to absolute scale performance estimates, such as cancers detected per 1,000 women, whereas in retrospective clinical studies, reader decisions do not affect patient management, and the multiple readers do read the same

case to gain statistical power. And there's the enrichment of case types, especially when the disease prevalence is low, such as breast cancer in this case. The reading conditions are well controlled, and some components of this may not be available in actual clinical practice. The makeup of studies is to compare two modalities. Here it's to compare 3Ds versus FFDM.

Therefore, controlled retrospective studies do not provide absolute measures of performance because of possible differences in case mix, reader training and experience, availability of prior images, patient history, and the reader mindset. However, it does provide meaningful and the least-burdensome comparison of two imaging modalities.

Some studies have been used to bring to market several imaging devices, for example, FFDM, DBT, and many CAD devices.

Some general considerations regarding ROC analysis. Clinical decisions are often binary, for example, call the patient back versus do not call the patient back. In the ROC methodology, the data collected are multiple levels of confidence in disease presence. The methodology is independent of decision threshold, which may vary substantially with user experience and training. ROC analysis and area under the ROC curve, or AUC, are consistent indicators of diagnostic information given to a physician, and it can be especially useful when one modality has higher sensitivity but lower specificity than the other.

Here is an example that was presented in the last Panel

meeting for the Hologic PMA, where the comparison was FFDM versus FFDM plus DBT. There were three studies associated with this comparison, and here I'll show the difference in sensitivity and specificity.

As you can see, in the first study, sensitivity and specificity gave an ambiguous comparison between two modalities, and they vary a lot across the three studies, whereas for the difference in AUC, it's consistent across the three studies.

Now I'm going to talk about specific aspects regarding the study design of this application.

One of the rationales to design the study objective is to look at a phantom. This table shows the ACR phantom dose per view. For Hologic FFDM, it is 1.2 mGy. And for this device, Hologic 3Ds, the dose is 1.45 mGy. And for the approved Hologic FFDM plus DBT, it is 2.65 mGy. And the average dose of FFDM, screen film mammography, and mammography CR, as collected from medical physicists' dose measurements available at the time of MQSA inspections this year, ranged from 1.43 mGy to 1.9 mGy. And the MQSA limit is 3.0 mGy.

So considering that the dose of Hologic 3Ds is comparable to that of FFDM and the average dose, and it's well below the MQSA limit, the study was designed as a non-inferiority study. The primary objective is to show AUC of 3Ds is non-inferior to that of FFDM with a non-inferiority margin of .05.

Secondary study objectives include AUC for subjects with dense breasts. Using 3Ds is non-inferior to that of FFDM with non-inferiority margin of 0.05. The non-cancer recall rate for 3Ds is non-inferior to that of FFDM with a non-inferiority margin of 5%.

Case selection. Inclusion/exclusion criteria for case selection provided by the Sponsor. Here I only highlight a few sub-populations that were excluded from the study. Those are patients with previous surgical biopsy, with placement of an internal breast marker, with breast implants or breast reduction surgery, and with breasts too large to be imaged with a single exposure.

Totally, 3521 subjects were enrolled in the study. But excluding 236 for training, we have 2985 eligible subjects. Then 300 subjects were excluded at the image acquisition site by applying the exclusion criteria, because of using incorrect technical tables.

Here I highlight that, among these eligible cases, about 20% of cases were excluded for image quality control issues such as patient motion or wrong positioning. Three hundred cases were excluded because of image QC for the FFDM, 171 cases were excluded because of image quality control issues in DBT, and 137 subjects for the wrong positioning of patients that would affect both FFDM and DBT. From these 2299 eligible subjects, 302 cases used for the reader study were randomly selected using stratified sampling.

Here I show the case selection categories. The first category is negative screening cases, which are the cases negative by FFDM reader and FFDM plus DBT reader at the image acquisition site.

The second category is the recalled screening cases. Those are the cases recalled by FFDM reader or FFDM plus DBT reader at the image acquisition site, but those are cases recalled and not sent to biopsy.

The third category is benign biopsy cases. Those are pathology proven benign cases. And the cancer cases are also pathology proven cases.

All four categories of cases were followed up for one year, and during that follow-up period, nine of the subjects were lost to follow-up, and one lesion that was initially categorized as benign was found to be cancer during the follow-up.

This table shows the number and the proportions of cases in these four categories for the current study and those tables in the original PMA study for reference purpose.

I would highlight two aspects that the Sponsor considered. First is that the proportion of recall cases was chosen to reduce potential bias in favor of 3Ds on non-cancer recall rate because most of recall cases are based on FFDM, and they're not necessarily recalled by the 3Ds. The second aspect is that the proportion of cancer cases was increased to gain statistical power.

As a result of these two adjustments, it is observed that in the

non-cancer categories, benign and recalled in that case, the proportion of benign and recall cases decreased from 60% to 33%, while the proportion of negative cases increased from 24% to 42%.

Because negative cases are relatively easier to be differentiated from cancer than that of recall cases, differentiating cancer from non-cancers may be easier for both the FFDM and the 3Ds due to the change of case mix, and therefore it is generally speculated that it may bias in favor of showing non-inferiority between FFDM and 3Ds.

This table shows the distribution by breast density. The Sponsor selected the category threshold between BI-RADS Breast Density Category 2 and 3. So nearly half of the cases are fatty and half of the cases are dense.

This table shows the distribution of calcifications versus non-calcifications. The cases presenting with only calcifications were considered the calcification group, and the cases with mass only or both mass and calcification lesions were considered with the non-calcification group. By design, the ratio of the number of calcification to the number of non-calcification lesions is roughly 1:2.

Characteristics of readers. Fifteen radiologists representing a range of clinical experience participated in the reader study. They are board certified, MQSA qualified, and they are trained in and familiar with the interpretation of digital mammography, and they're users of the Hologic

SecurView workstation. The readers received two days of training on the reading of 3D tomosynthesis with synthesized 2D images prior to the start of the reader study. The FDA requested that the statistical analysis be performed with all 15 readers.

So this is a fully paired acquisition, meaning that each patient got a combination of 2D FFDM and DBT. And the reading of the crossover reading to mitigate reading order effect, basically, for the first half of the cases the FFDM images were first read in Session 1 and the 3Ds images were read in the second session after one month. And for the second half of the cases the 3Ds images were first read and then the FFDM images were read in Session 2 after one month.

The following information was collected for each marked lesion: lesion location, probability of malignancy score on a 100-point scale, and forced BI-RADS score of 1 to 5.

The following information was collected for cases with no marked lesions: the probability of malignancy score on a 100-point scale, and a BI-RADS score of 1 or 2.

So, in summary, this was a controlled retrospective multi-reader/multi-case study on an enriched patient dataset with 15 readers and 302 cases, including 77 cancer and 225 non-cancer. The case dataset is enriched with different proportions of cancers or non-cancers than the general screening population. This is a two-session crossover reading

separated by a one-month memory washout period. The primary objective was to show AUC of 3Ds is non-inferior to that of FFDM with a non-inferiority margin of 0.05.

The missing data or lost patients could impact performance. As I showed you, about 20% of eligible cases were excluded due to image quality control issues. The protocol did not allow for repeat imaging on these cases. Nine of the 302 study cases were lost to follow-up. And the higher relative proportions of negative screening cases could favor the non-inferiority hypothesis. And the study excluded study sub-populations listed here.

So next, our statistician will present the study results and the robustness analysis of this missing data and the effect of case enrichment.

DR. YE: Good morning, everybody. My name is Jingjing Ye. I'm a mathematical statistician in the Division of Biostatics in CDRH.

Here's the overview of my presentation. I will go through the reader study results in the study for primary endpoint, secondary endpoints, and additional endpoints. Then I will go through additional robustness analyses. After that, I will have a discussion on case distribution and a summary of the results.

Here's a table for case distribution in this reader study. What's highlighted in red indicates the difference between samples with complete follow-up information and the samples in this reader study. There are nine samples lost to follow-up, eight in negative group and one in benign. I will

present the completer analyses results for the 293 patients, and the nine lost-to-follow-up patients will be addressed in additional robustness analyses.

The study endpoints in the study are the primary endpoint, AUC. 3Ds is non-inferior to 2D. The non-inferior margin is .05. There are two secondary endpoints, first, dense breast AUC. 3Ds is non-inferior to 2D. The non-inferiority margin is .05. For non-cancer recall rate, 3Ds is non-inferior to 2D. The non-inferiority margin is 5%.

There are four additional endpoints: calcification and non-calcification AUC, sensitivity and specificity, fatty breast AUC, and cancer recall rate.

All non-inferiority margins in primary and secondary endpoints are pre-specified. The additional endpoints were pre-specified. However, there were no hypotheses or non-inferiority margins pre-specified for these additional endpoints. Therefore, the results in additional endpoints are presented as descriptive statistics only.

This slide shows the average ROC curve for the primary endpoint, AUC. ROC curve is calculated using POM, probability of malignancy score. The pink line is the 3Ds and the blue line is 2D. The solid lines are the parametric fit done by the Sponsor, and the dotted lines are the empirical fit done by FDA. As can be seen from the plot, the parametric and nonparametric fits are close to each other.

The results of the primary endpoints are summarized in the

table. Both nonparametric and parametric fits using DBM method are done. The AUC difference between 3Ds and 2D are .036 and .041 for nonparametric and parametric, respectively. The 95% confidence interval lower bound is shown in the parentheses. The p-value for non-inferiority is highly significant. The non-inferiority margin is met for the primary endpoint.

For the secondary endpoint, dense breast AUC, here is the average ROC plot. Again, the pink line is 3Ds and the blue line is 2D. The solid line is the parametric fit done by the Sponsor, and the dotted line is the empirical fit done by FDA. The parametric and nonparametric curves are close to each other, but there seems to be some difference on 3Ds curves.

The results of dense breast AUC are summarized in the table on this slide. Both nonparametric and parametric fits using DBM method are done. The AUC difference between 3Ds and 2D are .05 for nonparametric fit and .045 for parametric fit. The 95% confidence interval lower bound is shown in the parentheses. The p-value for non-inferiority is significant.

Please note, the 95% confidence interval lower bound is not multiplicity adjusted.

The non-inferiority margin is met for dense breast secondary endpoint.

For the secondary endpoint, non-cancer recall rate, bootstrap results for random case and random reader, with respect to the case distribution, are summarized in the table. The difference between 3Ds and

2D is -14%, and the 95% confidence interval upper limit is -11.3%. These results are FDA's calculation and is different from the Sponsor.

Please note again, the 95% confidence interval upper bound is not multiplicity adjusted.

The non-inferiority margin is met for the non-cancer recall rate secondary endpoint.

This slide shows the results of average sensitivity and specificity. The results are done for a BI-RADS cutoff of 4. Thus, a BI-RADS score of 1, 2, and 3 are considered test negative, and BI-RADS 4 and 5 are considered test positive. Sensitivity increased .06 on average and specificity increased 10% on average.

This slide shows the change of sensitivity and specificity for individual readers. To take a closer look at that, here is the blow-up of the plot. Each line is for one reader. 2D is denoted by a circle. A triangle is 3Ds. The arrow indicates the direction of change from 2D to 3Ds. From the plot, specificity was improved for all readers, while sensitivity was improved for about half.

Here is the plot with average sensitivity and specificity. The thick black line indicates the direction of change for average sensitivity and specificity from 2D to 3Ds. As you see from the previous slide, average specificity was improved and average sensitivity was only slightly improved.

This slide shows the breakdown of the data for calcification and

non-calcification for the completer 293 patients.

Here are the results for the AUC for calcification and non-calcification. The AUC difference for calcification is estimated to be .036 and the AUC difference for non-calcification was .04. The DBM method with nonparametric AUC was used in the calculation.

For fatty breast, the AUC difference is estimated to be .024. Again, the DBM method with nonparametric AUC was used in the calculation.

For the last additional endpoint of cancer recall rate, bootstrap for random case and random reader was used in the calculation. The cancer recall rate increased .7% from 2D to 3Ds. This calculation is not lesion specific.

We have also done additional analyses of positive and negative likelihood ratios, PLR and NLR. Please note, PLR and NLR are not pre-specified endpoints. PLR is the ratio of true positive fraction to false positive fraction. NLR is the ratio of false negative fraction to true negative fraction.

The results of PLR and NLR are reported in the table, along with the bootstrap 95% confidence interval. Since PLR and NLR are not pre-specified endpoints, the confidence intervals are unadjusted.

PLR increased 1.22 from 2D to 3Ds. An increased PLR indicates greater positive predictive value (PPV) with 3Ds. And this increase is statistically significant. NLR decreased .04. A decreased NLR indicates

greater negative predictive value (NPV) with 3Ds, but this decrease is not statistically significant. The PLR and NLR results do not depend on prevalence.

As indicated earlier, there are nine patients lost to follow-up. Thus, the nine patients are unconfirmed non-cancers, eight in negative group and one in benign.

Several analyses scenarios are applied here. Under Scenario 1, you impute all nine cases as non-cancers. Under Scenario 2, you impute all nine as cancers. In worst-case scenario, you impute k out of nine cases with the highest POM, probability of malignancy, in 3Ds as non-cancers and the remaining nine minus k as cancers; k ranges from one to eight.

The robustness results are shown in the table. The three columns in the table correspond to the primary endpoint, AUC, and two secondary endpoints, dense breast AUC and non-cancer recall rate.

The first row in the table is the completer analysis shown in the previous slides. The second row is the analysis when all nine are imputed as non-cancers. The third row is the analysis when all nine are imputed as cancers. The fourth row is the worst of all worst-case analyses we scored, and the worst is one k equals three. That means three is the POMs in 3Ds as non-cancers and the remaining six as cancers. The results show that the estimates are close to each other. Thus, primary and secondary endpoints are robustness to unconfirmed non-cancers.

There are large proportions of patients excluded because of QC fail. Specifically, 21% of non-cancers were excluded because of QC fail, and 19% of cancers were excluded because of QC fail. If the patients were allowed to be reimaged, they could have been candidates to be randomly selected into the study.

To evaluate the impact of QC exclusion, we also ran some robustness analyses. Two imputation assumptions were evaluated: missing at random (MAR) and non-ignorable missing.

For missing at random imputation, we assumed the distribution of patients excluded by QC is the same as distribution of patients in the study, given disease status. The primary objective is still met under MAR assumption.

For non-ignorable missing, the distribution of patients excluded by QC is different from the distribution of patients in the study. For the two approaches, we scored using the non-ignorable missing imputation. The primary objective was met in one but failed in the other one.

For more details, I have backup slides to gain more detail.

As indicated in Dr. Chen's presentation earlier, the case distribution in this study may favor non-inferiority design. We then reweighted the case distribution according to the previous PMA to evaluate the robustness of the results. Therefore, cancer cases will change from 25% to 16%, benign decreased from 25% to 15%, recall increased from 8% to 45%,

and negative decreased from 42% to 24%.

The results of the primary endpoint, AUC, is shown in the table. The first row is Scenario 1, where all nine lost to follow-up were imputed as non-cancers. And the second row is the results after reweighting according to the previous PMA. The results were done by using random reader and random case bootstrap approach. The results show that the non-inferiority margin is still met for the primary endpoint, AUC, after reweighting.

The summary of the statistical analysis results are for completers. Excluding the nine lost to follow-up, the pre-specified non-inferiority margins were met for the primary analysis of AUC difference with a margin of .05, the secondary analysis of dense breast AUC difference with a margin .05, and the secondary analysis of non-cancer recall rate with a margin of 5%.

Classifications favored device use. Non-cancer recall rate decreased by 14%. Cancer recall rate increased by .7%. Likelihood ratios indicate increases in PPV and NPV.

Study conclusions of AUC non-inferiority appears to be robust to nine unconfirmed non-cancers, robust to QC exclusions if MAR assumption is assumed, but not if non-ignorable missing is assumed, and robust to choice of case distribution, in terms of proportion of cancer, benign, recall, and normal.

Next is Dr. Gary Levine.

DR. LEVINE: Good morning, everybody. My name is Dr. Gary Levine, and I'm a radiologist with the FDA.

To give you an overview of my talk, I'm going to discuss clinical significance, study design, study results, benefit versus risk, labeling and reader training, MQSA issues, and then I'll summarize my talk.

First some background. Tomosynthesis is the generation of slice images by digitally processing X-ray images obtained at multiple angles. The synthesized 2D images are a mathematical reconstruction from the 3D image set similar to a maximum intensity projection, or MIP.

Advantages of 3D over traditional 2D images are that (1) it reduces visual clutter by removing overlying anatomic structures, and (2) it allows for depth localization.

The original PMA approval studies support the benefits of 2D plus 3D for breast cancer screening and diagnosis, as was previously discussed this morning.

Next, I'm going to talk about clinical significance.

The 3D synthetic, as was previously discussed, is the 2D plus the -- excuse me -- it is the 3D tomographic acquisition plus the synthetic 2D. And this is a new exam option with a radiation dose that is comparable to current full-field digital mammography. Using the 3D synthetic option could reduce the radiation exposure and slightly reduce the compression time by eliminating the FFDM acquisition required with the current 2D plus 3D exams.

And we have repeated the numbers here, and as you can basically see, using the synthetic 2D, we have 1.45 mGy versus the average measurement from physicist dose measurements available at the time of MQSA inspections performed from January to September of 2012. And 1.43 mGy and 1.45 mGy are very comparable, as a practicing radiologist and electrical engineer.

I'm going to talk a little bit about the study design, and basically I'm going to review what's already been discussed earlier.

The study design is similar to the multi-reader/multi-case studies used to support the initial digital breast tomosynthesis approval. And this is a stratified sampling to obtain representative enriched dataset based on lesion type and breast density. This study was performed using 15 board certified and MQSA qualified radiologists. Readers and cases were not used for any prior studies, so these were all new cases. And the study was set up as a non-inferiority study, since the 3D synthetic exam dose is comparable to the existing average 2D full-field digital mammography dose, which is the current standard of care.

The study population was a mix of routine screening and patients scheduled for biopsy. Cancer truth is based on biopsy results, whereas non-cancer truth required a one-year follow-up mammogram. And follow-up on 9 of 302 cases is missing, and as a practicing radiologist, this is not particularly worrisome, and this is a common occurrence. The case

distribution, to summarize, was 77 cancers, 24 recalled screening cases, 75 benign biopsies, and 126 screening negatives. So this is obviously an enriched set.

Study results. The 3D synthetic was non-inferior in the receiver operating characteristics area under the curve compared with full-field digital mammography. And this was already discussed by multiple prior presenters.

Secondary analysis indicates a reduction in the non-cancer recall rate. Secondary analysis also compared the 3D synthetic examination to the 2D full-field digital mammography across both fatty and dense breasts, non-calcifications and calcifications, across sensitivity and specificity, and across cancer recall rate.

Benefit versus risk. Compared with FFDM in clinical practice, the 3D synthetic may reduce the number of non-cancer recalls, which is thereby going to reduce patient anxiety and radiation dose from additional imaging, and I think it will make most of the women being screened happier at the end of the day. However, the 3D synthetic exam will not include the standard of care FFDM images, which will impact how mammography is performed and interpreted. And from a practical workflow viewpoint, this may require some minor tweaking.

Continuing with benefit versus risk, compared with the approved 2D full-field digital mammography plus 3D digital breast tomosynthesis option, when using the 3D synthetic option, there will be

lower radiation dose compared to the combined 2D full-field digital mammography plus 3D digital breast tomography. It should also be a slightly shorter breast compression with the 3D synthetic.

Labeling and reader training. And this is an important area. The labeling states that the synthesized 2D are only to be used as an aid to the 3D images. And this reflects the intended use and the study design. And we do feel the labeling should reflect both the intended use and how the study was designed.

Continuing with labeling and reader training, users need to understand that the synthesized 2D is similar to, but, because it's a mathematical reconstruction, it is not identical to standard of care 2D full-field digital mammography.

Note, however, the images will also contain the C-View mark, so it will be obvious to the interpreting radiologist, as well as the performing technologist, that this is in fact synthetic.

The software used to create the synthesized images depends on certain assumptions about the breast geometry. Therefore, the training should include how synthesized 2D images might look different and how to account for those differences when comparing to prior full-field digital mammographic exams.

The labeling and training should inform the radiologists and technologists of situations when to acquire the current standard of care 2D

full-field digital mammogram instead of using 3D synthetic. The labeling states the following situations that could result in atypical synthesized 2D images. These include large artificial objects such as implants, pacemakers and port-a-caths, diagnostic paddles, intramammary metallic markers, patient motion, mastectomy view, or a surgical specimen.

The study, by design, excluded subjects with an internal breast marker, breast implants, and breasts too large to be imaged with a single exposure. These situations may not match all of the assumptions used by the software and could result in atypical synthesized 2D images. Therefore, we at FDA expect the labeling to address that the performance of 3D synthetic in these situations was not established by design in the clinical trial.

The study excluded subjects with previous surgical (excisional) biopsy. This exclusion was by design to avoid confounding the results. This exclusion is not addressed in the labeling, and therefore we at FDA bring this up for consideration for Panel discussion under Question Number 3.

MQSA requirements. This first slide is adapted from the original approval.

Tomosynthesis is being treated as a new mammographic modality requiring that all personnel -- and that would include radiologists and technologists -- obtain eight hours of training in that mammographic modality prior to use on patients. Hologic must provide each facility with a quality control manual clearly defining initial, periodic, and yearly testing

requirements. And it is also anticipated that facilities will follow the manufacturer's quality control, or QC, manual.

Continuing with MQSA requirements, the synthesized 2D view will not be treated as a new modality. The training for the synthesized 2D views can be included as part of the eight-hour training for new users of tomosynthesis. MQSA will also continue using the certificate extension program for the immediate future for accreditation.

All right, I'm going to summarize this.

The study design is consistent with other multi-reader/multi-case mammography studies. It is difficult to establish the clinical benefit-to-risk ratio from an enriched stratified sampled study. And this is true pretty much of any study of this nature. The results are non-inferior to full-field digital mammography, but indicate the likely benefit of using the 3D synthetic to reduce the recall rate. The dose is comparable with current full-field digital mammography, so there is minimal additional risk.

Hologic needs to provide training to help new users utilize the new technology effectively. And we at FDA expect the labeling to address situations where the currently approved full-field digital mammography and/or full-field digital mammography plus digital breast tomosynthesis screening options may be more appropriate instead of using the 3D synthesized view, which, as I said before, is 3D digital breast tomography plus a synthetic 2D view.

And I'll turn it back over to Dr. Ochs.

DR. OCHS: Thank you.

Now I'd like to give a brief background of some of the issues we'd like the Panel to discuss this afternoon.

First, as noted, the standard of care FFDM images will not be acquired with the proposed 3Ds option. FDA would like the Panel to discuss aspects of performing and interpreting mammography that should be considered in the training and labeling. For example, the Panel could discuss the use of 3Ds for comparing current and prior exams.

The second topic is the study biases. The study design is similar to the other MRMC studies. Potential biases with the current study include the distribution of cases, which could favor the non-inferiority hypothesis, cases being excluded from random selection because the image set did not pass the QC criteria, and lack of confirmation of eight negatives and one benign as non-cancer because they were lost to follow-up.

FDA would like the Panel to discuss any concerns with the potential sources of bias and if the presented analysis on the robustness of the results is sufficient.

For the third topic, we'd like the Panel to discuss the study exclusions. The labeling addresses some study exclusions, such as breast implants, that could cause atypical images. However, there is no information to indicate that subjects with previous surgical (excisional) biopsy will cause

atypical images.

In the original Hologic PMA approval for tomosynthesis, subjects with surgical (excisional) biopsy were excluded by design to avoid confounding the results as prior patient studies and reports were not available to the reader.

The results were considered generalizable in that situation for the original PMA since there were no technical concerns with imaging these subjects and the FFDM images and patient history would still be available to the clinical users. FDA would like the Panel to discuss the generalizability of 3Ds to subjects with previous surgical biopsy.

And then the final topic is rather broad. We'd just like the Panel to discuss any other concerns with respect to the safety, effectiveness, or benefit/risk associated with the proposed expansion to the indications for use of the system.

Thank you.

DR. ROSENBERG: I would like to thank the FDA speakers for their presentations.

And does anyone on the Panel have a brief, and it's clarifying, question for the FDA? We'll have time for other discussions. And please remember that the Panel may also question the FDA during the Panel deliberation sessions later this afternoon.

So brief clarifying questions. I guess I can repeat things and

start on that side of the table.

Could someone, maybe Lori, explain what is a non-inferiority margin? That's not a radiology term.

DR. DODD: This is Lori.

So the non-inferiority margin is used when there are two things -- well, there's a standard of care, and something else that's experimental, either a treatment or a device, and it's thought that the two devices would be close in terms of their -- in this case, in terms of their performance with regards to the area under the curve.

If we want to prove that two things are identical, we need an infinite sample size, and we can't do that. So what we specify is a non-inferiority margin which says if we can prove that the area under the curve is at least of this magnitude worse than the existing device, that we will consider these two to be roughly the same or that the new device is not inferior to the existing device.

DR. ROSENBERG: Thank you.

Was that okay, Janine, to ask Dr. Dodd?

(No audible response.)

DR. KRUPINSKI: Elizabeth Krupinski.

There was a slide that was talking about the non-ignorable cases, and you said you had a better explanation because, on the slide, it said the results were mixed, but then the speaker specifically said failed. And so I

was wondering if you could show us those additional slides and explain a little bit more about those non-ignorable cases and the analyses and why it failed.

DR. YE: Jingjing Ye.

I can show how we actually incorporated those samples that are excluded by QC into the study. So here's the diagram that shows the full chart of the samples in the study excluded by QC.

Just as a reminder, 79% eligible to be randomized into a study for non-cancers, 21% excluded for cancers, 81 eligible for random selection, and 19 excluded.

So if we go to the non-ignorable missing, this is going to show how we bring the patients excluded by QC into the study. So if you see here, the non-cancer cases will be split into X_1 and Y_1 cases here.

So the X_1 one is the patients who are eligible to be randomly selected in cancers, and this now only accounts for 79% of non-cancers in the study. And Y_1 is the cases excluded by QC and there now accounts 21% of non-cancers in the study. So combining X_1 and Y_1, they together account for 225 non-cancers.

And similarly for cancer cases, they are going to be split into X_2 and Y_2. And the X_2 now accounts for only 81% of cancers in the study and Y_2 are the patients excluded by QC and they accounted -- they will account, on average, 19% of cancers in the study. So then, combining X_2 and Y_2, they account for 77 cancers in the study.

And the POM score, the probability of malignancy, is missing for those Y_1 and Y_2. So the way of how we're going to impute that is assuming non-ignorable missing. Basically, one way to do that is to impute Y_1 and Y_2 by random sampling of POM scores by pooling non-cancers and cancers together. That means, for all 302 cases, they're not specific to cancers or non-cancers. So in this way disease status of cancers and non-cancers of those QC fail patients were not informative for all readers. So, in this way, it is conservative against the device.

So this slide shows all the results. So the first row is the Scenario 1, which has nine lost-to-follow-up patients as non-cancers. The second row is a Meier imputation, which is missing at random. And the last two rows, two scenarios, will support using non-ignorable missing.

So the third row is the non-ignorable missing on both 2D and 3Ds, which implies that patients excluded by QC by either 2D or 3Ds are different from the patients in the study.

And the fourth row is MAR on 2D and non-ignorable missing on the 3Ds, which implies that patients excluded by 2D QC are similar to those in the study, given disease status. However, patients excluded by 3Ds QC are different from those in the study.

So as you can see the AUC on the results, we used AUC difference. The two cases for non-ignorable missing, one still met the primary endpoint and the other one did not.

DR. ROSENBERG: Okay. I'm sorry, please.

DR. WATSON: Karol Watson.

DR. ROSENBERG: Yeah, Dr. Watson.

DR. WATSON: I just wanted to make sure I understood this. It looks like the fourth line really does bias it against the device. Am I correct in that?

DR. YE: Jingjing Ye.

Yes, it's a way to conservative against the device. Yes.

DR. WATSON: Thank you.

DR. ROSENBERG: Seeing no further --

DR. DODD: Wait.

DR. ROSENBERG: I'm sorry. Dr. Dodd.

DR. DODD: This is Lori.

I just want to ask a follow-up question. I'm trying to get my head around the -- I mean, I can understand that it's an extreme setting and an extreme case of potential bias, but is it even realistic? Does it tell us anything about whether this is a likely scenario? I mean, it seems very extreme.

DR. YE: Jingjing Ye.

I think the assumption here is not easy to justify whether it is realistic or not. We just want to provide a conservative estimate against the device. You see how robust the results are for the primary endpoint, AUC.

And I think this imputation, although it is against the device used, but if you consider those patients excluded by QC, those patients are also part of the intent-to-diagnosis population. So we want to bring that in, and this is one way of bringing that into this analysis.

DR. FAULK: Dr. Faulk.

And I have a question for the FDA. I don't know if this is necessarily a clarifying question, but I'm going to switch from the leaves to the forest for a second.

As a practicing radiologist specializing in breast disease, I read over 12,000 mammograms a year, and I have a very varied practice, which includes inner city, suburbs, rural, as well as low income and minorities. My real world is that I have many patients with large breasts, I have many patients with implants, many with tissue markers, and in addition, if I look at my practice, probably 10% or less of my patients are new patients as opposed to established patients.

My point and my question for the FDA would be what proof or reasonable evidence can be made that the results of this study are transferable to the general population?

DR. ROSENBERG: Volunteers?

DR. OCHS: I think, in a sense, that sounds like a question for the Panel that we're bringing to you is, you know, are you comfortable with the results and the generalizability?

I think from our standpoint, from more of a regulatory standpoint, you know, we want to see that there's consistency in the study design and in the final device labeling.

And so, again, if a patient population was excluded from the study design, we need to think to ourselves, well, why was it excluded? Is there a technical reason? Is there potentially going to be a clinical difference with this patient population? So that's our consideration. And then, once we kind of get a better idea of what was excluded, then we have to think, you know, what evidence is necessary for using the device with it.

And so it's not an easy question. It will depend a little bit on what the exclusions are and what the issue is and what the Sponsor, of course, is willing to do, too. I mean, again, there are some instances where we'll just add a caution statement or a precaution in the labeling, saying this patient population was not studied and that it's going to be up to your discretion, as a practicing radiologist, whether or not to use the device with that patient population. It's a complicated question. It's a good question, but it is complicated.

DR. ROSENBERG: And that can be also a discussion within this group.

DR. FAULK: Yeah, we don't ask the easy questions.

DR. ROSENBERG: Further questions?

(No response.)

DR. ROSENBERG: Okay, it's now -- I have 11:01, so we can take a 10-minute break. A reminder. Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any member of the audience. And we will resume at 11:12.

Thank you.

(Off the record.)

(On the record.)

DR. ROSENBERG: It is 11:15. I think that's about what I said.

We will now begin a portion of the meeting where we, as a panel, will deliberate amongst ourselves. I want to open the floor to the experts around the table to begin deliberating on any issues that you may have with any data you've heard today, either this morning in the panel discussions or discussions with the FDA and the Sponsor, or the material that you have read in your Panel packets.

So this could be quick. So any questions?

Dr. Hooley.

DR. HOOLEY: Regina Hooley.

I think I'll just look at my notes. Okay, the proposed unit can perform three different types of exams, and I assume that, from those users and from those patients, the exam, such as screening exam as well as the diagnostic exam, will start with a tomo.

How will the choice be made regarding the use of the 3Ds

versus the 2D combo, assuming that the patient does not have implants or any manmade devices or a diagnostic paddle is not going to be used?

There's no thorough study comparing the 3Ds with a 2D combo. From what I've read, the 2D and 3D combo might be slightly superior. Although the radiation dose is higher, it's still within acceptable limits.

So will this decision be made by the radiologist? Will this information be given to patients? Will they be able to choose? Or will it be a random event or will the FDA have specific recommendations on its use?

DR. ROSENBERG: Janine.

MS. MORRIS: I'll just ask one of my staff members to answer.

DR. OCHS: This is Robert Ochs.

So Hologic is requesting approval for the option. So from our perspective, we want to make sure that Hologic can provide adequate training and information to help radiologists decide what exam is best for their practice and again, in discussion, I guess, with their patients as well, how to select the best exam for them.

When we're doing a study, we're looking at this exam option. Is there a reasonable assurance that this exam option can be used? And so we're not necessarily trying to compare with every other exam option out there. We're just trying to compare with the standard of care FFDM. And so that's how this study was designed, for a new option for radiologists and patients.

DR. HOOLEY: That answers my question, but it's still not very specific. It's an option. But some patients are very informed, and some patients can think they're informed but they're actually misinformed. And so when this information gets out to some patients, you know, they might want to have a choice, which I suppose is acceptable. It is acceptable.

But I still would like to see, eventually, a comparison between the 3Ds and the 2D plus a 3D combo. I know that the 2D plus a 3D combo is not the gold standard, it's not the standard of care, however, it is a very high level of mammography and has superior diagnostic accuracy. So I would like to see a comparison so that maybe we can raise the bar even further going forward.

DR. ROSENBERG: Dr. Faulk.

DR. FAULK: Yeah, probably a question for Hologic and maybe some other members of the Panel.

Is it reasonable to assume that some cancers are detected at 2D that are not detected at 3D?

DR. ROSENBERG: It looked, from the results, as if there were cases in which sensitivity went down for, at least, individual readers.

DR. FAULK: Yeah, I would agree. And I guess where I'm going with this is the following, that if it's reasonable to believe that there are some cancers that are detected by 2D initially and then maybe evaluated by 3D and are not seen by 3D, whatever the case may be, then the next question would

be, does the C-View -- how does the C-View image compare with the 2D full-field digital mammogram?

Because the issue would be, if you're looking at things that might be probably detected at 2D but not 3D, such as asymmetric opacities -- one thing not mentioned here was developing densities, which of course couldn't be evaluated because there are no comparisons, but that would be another thing that probably would be better seen on 2D as opposed to 3D.

So the question mark then is, is that if -- under the way this is proposed now, that a final or -- I can't remember the exact way you termed that, but the decision could not be made on the case based on 2D alone. So if the detection is only on the 2D and you're comparing it with a conventional 2D digital image and we don't know how those two actually stack up, then, if a cancer is -- is it reasonable to assume that a cancer could be missed on the C-View 2D image?

Because where I'm ultimately going with this is that if you lose some detection on the synthetic 2D image that would've been seen on the full field DM, then, if you missed the cancer, what is your legal basis for missing that cancer?

DR. ROSENBERG: Other radiologists on the Panel have any comments?

I think you're basically getting into the question of what is the difference between the synthesized image and a full-field digital image in

interpretation, which could also include comparisons. In other words, we use that as part of our routine.

I don't know if anyone on the Panel has comments or thoughts about differences using the synthesized images for comparisons currently or in the future.

Hologic, FDA, is there any comment you'd like to make about the issue of are we losing or gaining anything by the synthesized images as compared to the standard full field images? And in particular, I think what's not been addressed yet is as comparisons.

DR. RAFFERTY: Thank you. Betty Rafferty.

In addressing this question, you brought up several different elements. First, if you recall, we're looking at the 3D plus C-View. That means that you're able to use the totality of the information from the two examinations.

So while you don't want to interpret the C-View in isolation, you're going to get the synergistic benefit of the two. What I mean by that is, if you see something on the 3D, such as a density differential, some sort of a developing density or developing asymmetry, if you will, then you go the 3D dataset and you look for the correlative finding on that 3D dataset.

I will say that, as a user of tomosynthesis in clinical practice, most of these cases of developing asymmetry, which is a fairly unusual presentation of a cancer, I'll just say, turn out to be a mass on tomosynthesis.

And so you appreciate that right away. That's why it's important that the two function together as one.

Basically, the current comparison was of 3D plus C-View to the current standard, which everyone's acknowledged is 2D FFDM. And the technology, 3D plus C-View, performed in a superior manner to 2D FFDM.

So while I'm sure, based on all of our collective experience, that we can all point to a single case to inform any specific situation, I think the evidence that we presented is fairly compelling that the 3D plus C-View actually behaved better.

And the reason that it probably did -- this is my opinion -- is from the tomosynthesis element, from the fact that you're able to much better see those masses and distortive architecture. And that represents a real benefit for patients, because the types of cancers that you tend to see on tomosynthesis are masses and distorted architecture, which generally represent invasive cancers as opposed to calcification-type cases, which more generally correspond to DCIS.

Does that help with that?

DR. FAULK: Yes, I think that helps clarify it. I think the issue for me would still be that the synthesized, the C-View image, on your study, if there was detection initially on the synthesized 2D image, I guess what we don't really know is how does the synthesized 2D image really stacks up by itself against a 2D image, because perhaps you're missing things on the

synthesized image that would've been seen on a conventional FFDM. If you don't know the answer to that --

DR. RAFFERTY: Yeah, that's true. But the real question is, are you missing anything on the combination of the synthesized image and the 3D dataset that would've been found instead on a standard FFDM? Because you're never going to be asked to look at just the one in isolation. You're always going to have all of that available to you.

And I'll also say that another peculiarity is that when we did our prior PMA submission for 2D plus 3D, I think what we didn't expect was that in clinical practice it would actually perform better than it did in the reader study. But that was definitely the case. It performs better in clinical practice than it did in an enriched reader study, which was not my expectation.

So I would just say that this is an important option for women, particularly who are concerned about the radiation risk of the combo imaging. And there are women and practitioners out there who are concerned about this, and for them, this is to me a clearly better option than a standard 2D FFDM mammogram.

And in some of these exclusion cases, like the women with large breasts and the women with implants, those women with implants are already getting eight images as their standard of care in an FFDM. This allows them the option to take advantage of tomosynthesis at a lower dose. And the same holds true with women with large breasts, which need multiple

exposures in order to completely tile the breast.

So I think these are important things to consider with respect to the population at large and the potential benefit.

DR. ROSENBERG: Yeah, thank you, but that was a little bit beyond the question we addressed to you.

Dr. Simon.

DR. SIMON: Dr. Simon.

I was just going to say that the study that perhaps wasn't done would be to look at just the C-View in a direct comparison only to full field. But it wouldn't make sense because, when Dr. Rafferty presented it, she said you only get the C-View because you've done a DBT.

But the one point I was going to refer back to, and it touched on maybe Dr. Hooley's comment, you had showed Slide 9, out of Norway -- I don't remember the name of the doctor who presented at RSNA. But on that slide, if I'm correct, you had -- the data breakdown there actually showed full-field digital, 3D, and then the combination of full-field digital plus 3D, is that correct on that slide?

DR. RAFFERTY: Yes.

DR. SIMON: And did it also show 3Ds on that slide?

DR. RAFFERTY: Yes.

DR. SIMON: And what we've seen on that slide -- and I don't remember the exact numbers, but it looked like the highest detection rate

was with full-field digital plus 3D, correct? There was a little bit of gain there.

DR. RAFFERTY: Yes.

DR. SIMON: Okay. I mean, that sort of addresses, I think --

DR. ROSENBERG: Would you come on up so we can get this in the transcription?

DR. RAFFERTY: I'm sorry.

DR. SIMON: I mean, if you could just -- I thought it could've been -- I mean, we're offering patients here, or offering doctors here, a transaction, which is we're going to do away with these full field images, potentially, and in exchange for doing away with that, you're going to get DBT plus the 3Ds images, and that's the transaction.

DR. RAFFERTY: Um-hum.

DR. SIMON: Ultimately, when the transaction is made, we're going to move the ROC curve up into the left. But you only get that because you get the whole transaction. What we're giving up, we're not certain because it didn't get done as the study, is what's the direct comparison between full-field digital images, CC, MLO, and you know -- and you sort of alluded to this, Dr. Payne, when you said you're giving up something by not having full-field digital. You're giving up some line resolution. But you pick up --

DR. RAFFERTY: I would agree that they are not exactly the same, as Dr. Payne said. In terms of what you're giving up, I guess, from my

perspective, we only have the data that we have to look at, which is the comparison of the performance of those two imaging techniques.

DR. SIMON: Okay, that it improved. Except for Number 7, largely, it improved.

DR. RAFFERTY: Right.

DR. SIMON: Yeah.

DR. RAFFERTY: I think that's real world.

DR. SIMON: And I agree, actually. I thought the curve moved up, the ROC curve moved up to the left. I mean, it sort of speaks for itself. But actually to touch on Dr. Hooley's point, you know, sort of an additional benefit, it would come again, to look back at the transaction with more radiation. You know, it's like there's no free lunch. You also get what you pay for. If you put more radiation --

DR. RAFFERTY: With the 2D plus 3D combo.

DR. SIMON: Correct.

DR. RAFFERTY: Um-hum.

DR. SIMON: But could you just talk about -- because we didn't discuss it, how 2D or 2D plus 3D combo, what those numbers were versus 3Ds? Because you had it on for one minute when you had that slide up. I think you remember it.

DR. RAFFERTY: Correct. I think that there was a difference of two cancers. It might've been something like 39 to 37. So again, interim

analyses --

DR. SIMON: It was Slide 9.

DR. RAFFERTY: Oh, I'm sorry, it was 29 to 27. A little inflation on my part. So there are 29 cancers on 2D plus 3D, 27 on 3D plus C-View, which is the technology we're looking at, 21 on 2D plus CAD, and 20 on 2D. So if you look at 2D, it was 20. If you look at 3D plus C-View, it was 27. If you look at the combination imaging, it was 29.

DR. SIMON: Right.

DR. RAFFERTY: And, again, these are small numbers. So I think, as I said, we would want to await the final study outcome, where numbers will be larger.

DR. ROSENBERG: Dr. Krupinski.

DR. KRUPINSKI: Yeah, Elizabeth Krupinski.

I guess this is a question for the FDA. On one of your slides you talked about labeling, and it kind of gets back to what Dr. Hooley was talking about. And so how do you decide in advance which patients go this way? And one of the criterion in there that you listed as labeling that could affect the results or result in atypical synthesized 2D images was patient motion.

I mean, how on earth do you decide in advance whether or not a particular patient is going to be affected by patient motion? And given that this is a little bit longer of an exam, how do you see that impacting things, and how do you take this into account?

As a practicing practice, is it the tech that makes -- getting back to the initial question, is it the tech that decides in advance? Is it the radiologist? Is it based on a patient's age? Did they look frail, they can't stand?

So if this is going to be part of the labeling, I'd like to know how you foresee people incorporating that into their decision-making strategy.

MS. MORRIS: Let me see if one of my staff are prepared to answer that for you.

DR. ROSENBERG: Okay, I think Dr. Watson was next.

DR. HOOLEY: Can I address that question from a clinical point of view?

I think that in some cases, a technologist can anticipate that there will be patient motion. For example, if someone has a disease like Huntington's disease or Parkinson's and they're trembling, then you would know that there's going to be significant motion. But other times maybe not --

(Simultaneous speech.)

DR. KRUPINSKI: I can see the extreme cases, yeah. In a normal situation, like with a new patient coming in --

COURT REPORTER: Try not to speak over each other.

DR. KRUPINSKI: Okay.

DR. HOOLEY: In some cases you can tell in advance. In some

cases you cannot tell, but that's also true with 2D full-field digital mammography as well. So if there's motion, they might have to be repeated, which we do now as a standard of care. And at least the dosage in this case would be nearly equivalent.

DR. ROSENBERG: Ms. Morris, do we have an answer?

MS. MORRIS: Yeah, Dr. Levine is going to give you an answer.

DR. ROSENBERG: Thank you.

DR. LEVINE: Hi. Gary Levine, a radiologist with the FDA.

As you have mentioned, Dr. Hooley, there are many clinical variables in practice. You always have the option of going back and doing a 2D standard of care full-field digital mammogram. We don't want to be so proscriptive as to restrict the practice of medicine, and it will just evolve over time where the technologist and the radiologist -- and like you mentioned, where the technologist just thinks this person is likely going to move, then you may want to choose to go ahead and do that.

Now, in the screening situation where there's no on-site radiologist, the technologist might make the a priori decision. The radiologist can always retrospectively say hey, there's motion. And whether it's from an upper GI to a mammogram to an MR of the shoulder, we've all seen motion. Sometimes we decide there's a recall. We bring the patient back and we get another set of images, and sometimes we decide it's good enough. But there's always the option to go back and do the standard of care 2D FFDM.

And so we're kind of leading that into the realm of practice of medicine, and so that each practice will in essence have to figure out when they want to use the 3Ds and in what situations. And in some senses, for screening, the technologist, if there's no radiologist available, which commonly happens in smaller clinics out there, the technologist will have to make the a priori decision at that point, and when the radiologist comes back and reads it, they can always say okay, there's too much motion. I want to bring this patient back and get the standard 2D. And you can't imagine, up front, every possible clinical scenario when you design a trial.

Nonetheless, from a public health standpoint, where the focus is safety and effectiveness, we feel it should be labeled so that the practicing radiologist is aware of what was studied in the trial and what was not studied and then just leave it up to each clinic and each practice to decide what's going to work best for them and their patient populations, because there is a lot of variability in patient populations across the country.

DR. ROSENBERG: Yeah, actually I had a question, I think, for Dr. Levine, also. A trial question.

Unlike the prior trial where standard images were available and therefore, whether there were comparisons or not, it would be equivalent, is there any reason to believe that the trial would've been different in its results if there were comparisons available, which is how images are routinely reviewed? So it's a trial question.

DR. LEVINE: Right. Well, I can give you a clinical answer. Prior images were not available because that's the way the trial was designed. In practice you and I, Dr. Rosenberg, both know we always want old studies, and we not only want the mammogram from a year ago, we'd like it from two and three years ago because subtle changes show up better over larger time intervals. They just simply designed the trial this way. And so we feel that the labeling should reflect the way the trial was designed.

Now, you can always come back and design a different trial and come back with an additional submission through the appropriate regulatory pathway.

DR. ROSENBERG: I was just asking whether there's any reason to believe a difference in the results, if there were comparisons available, it'll be a differential between the synthesized images and traditional priors. That seems to be the question.

DR. LEVINE: I don't think we have data to answer that, so I don't think we can answer it in a regulatory science format.

MS. PRICE: Carol Price.

I have a question in regards to the labeling. You're talking about this going to the radiologist. What about in the communities where it's your private physicians that are ordering these tests? It's not a radiologist. How are they going to get the information to start the process of which test they have done?

DR. ROSENBERG: Any comments?

Ms. Morris.

MS. MORRIS: Dr. Barr will answer.

DR. BARR: Helen Barr, FDA. I'm the head of the MQSA program.

What I foresee is that the OB/GYN would order a screening mammogram, and then the practice will decide. In my facility, a screening mammogram for most women is option X. I don't foresee that people other than radiologists would be making that decision.

DR. WATSON: As a referring physician -- Karol Watson -- I completely agree with what you say. We order screening mammograms and the radiologist decides.

MS. PRICE: Carol Price.

What about the public, then? How does the public get the information so that they are able to talk about this with their ordering physician?

DR. BARR: You know, that's a tough question. I think the public will get it -- I think women will get it when they come to the facility and the facility says this is what we do now. And then they can speak to the radiologist if they have questions. And then, in feedback, the referring clinicians, as this feedback mechanism occurs and they get reports on this, they may learn more.

Where I practiced in Kaiser, we could give a seminar to all the physicians in private practice. Obviously that's harder, but it could be done in HMO settings or hospital settings to teach clinicians about this.

DR. ROSENBERG: Is this also a labeling issue in terms of how the device can be portrayed? Is that an FDA issue?

Ms. Morris.

MS. MORRIS: So FDA's authority is to look at a reasonable assurance of safety and effectiveness to allow the product to be used, and part of that authority is to look at what is appropriate labeling.

And I would like us, as FDA representatives, to refrain from answering some of these broader questions, because that's the purpose of the meeting today, is to hear from our experts about what are the concerns.

The company has put together a dataset that has been evaluated and what are the additional implications. And then we can work with that in terms of our regulatory authority. If that means enhanced labeling, if that means increased training, other mechanisms, then we can try to apply those. But we really need to hear from the Panel.

DR. ROSENBERG: So you want our input as to what might be appropriate labeling, okay.

I think Dr. Faulk and then Dr. Smith. Yeah, and then we'll go down the line.

DR. FAULK: Dr. Faulk.

I guess I'll address the labeling and exclusions for a minute, I think, from the practical standpoint. I think the analogous situation is occurring right now with the dense breast issue that we're facing in clinical practice.

I can just tell you that, from the dense breast standpoint and adjunctive screening for women with dense breasts, which is becoming progressively more of an issue and women are becoming in tune with it, it has sucked up a tremendous amount of radiologist time and tech time and decreased from productivity and created a lot of unhappiness.

The issue is, is that while you can give a woman a preprinted information sheet regarding the benefits and potential downsides of adjunctive screening, there's still a significant number of women you'll have to talk to individually in order to answer their questions about whether adjunctive screening is appropriate for them or not. And that is not a one-minute conversation. That's usually a 5-minute to 10-minute conversation.

So what I see coming down the pike with this, with the potential exclusions of do we just automatically exclude women with implants, women with tissue markers, women with large breasts -- because I can put out a printed sheet and say well, you know, this was not evaluated in the study and therefore we're not going to do them. But I can tell you, there will be women that challenge me for having read lay reports and so forth, and say well, I don't care if I have implants or not. I still want 3Ds. And then I'm

going to be sucked into a significant conversation with them.

So I think the way it is right now, I would find it very difficult. Unless I hear a reasonable way to address the labeling and the exclusions, I see a tremendous amount of misinformation and radiologist time because the primary care physicians or the physicians that order them are not in a position to address these issues.

DR. J. SMITH: Thank you. I'm Justin Smith.

I think that question that you asked about how does the public know about this, is astute. The challenge is balanced by what Dr. Faulk brought up of the practicality of daily practice, and the more time he spends explaining things to patients means the fewer patients he will see.

And I know that, at least in Washington State, our first job is to make sure that women who need mammography or screening mammography get it, because we have a long way to go there, particularly in our rural practices.

But the issue that comes up -- and it's a balance between not wanting to be paternalistic but also wanting to take responsibility and in some way protect the patient from the intricacies of medical imaging as it gets more complex, which is what you hope we would do. I look at it much like if I happen to be doing nuclear medicine and if I'm going to be reconstructing a particular case, do I use this filter or do I use that convolution filter? And it makes a difference in how the image looks, the

noise, the background, and so on. But it would be a waste of the patient's time, I think, and almost cruel to sit down and have a discussion about convolution filters, even though they affect the sensitivity and specificity predictive value and so on of the outcome.

What I'd like to see happen is something along the lines of a general notice that in a given practice, this is how we approach screening mammography. If you have questions, your questions are important, and we want to answer them, but the technologist will be happy to help you with that. And so I would tend to pitch this towards the technologist to answer, who, at least all of them that I've worked with, would be capable of giving a very reasonable overview for most patients. So that's how I would address that.

I would also want to make sure that the radiologists who are using this have access to at least an atlas of the artifacts that are associated with the synthetic images, because it's not that synthetic is necessarily bad or better or worse, as we've seen from the data, but it will be different. And when you have differences, there will be artifacts that are not expected with, say, the full field method. So I would also want to make sure that the radiologists are trained in what the artifacts -- what the range of artifacts look like are.

DR. KRUPINSKI: Elizabeth Krupinski.

I guess this is a question for Hologic and it relates to -- it's

vaguely tangential, but it relates to effectiveness and some of the issues that we were talking about in terms of generalizability and accessibility to patients and so on.

Is the currently approved system billed the same as a 2D FFDM, or is it a totally different billing code? And then would the new version be a totally separate billing code the same as or before?

And it gets to the question of whether self-paid patients and so on are able to access these newer modalities because of differential pay. If this is more expensive, then it impacts the effectiveness and generalizability as we're not able to reach out.

DR. ROSENBERG: Yeah, I'm not sure we can talk about billing issues here.

DR. KRUPINSKI: Talking about billing issues is tangential or --

DR. ROSENBERG: Yeah, I think billing issues are beyond our purview, but labeling is appropriate.

DR. KRUPINSKI: Okay.

DR. COLDWELL: Doug Coldwell.

I just had a couple of comments to make, from sitting back and listening and engaging my frontal lobe this morning. This seems to be new technology. This is very similar to, I think, when we started introducing CT, because CT is basically a synthetic image. So I think that the practices will adapt, and I think it's probably going to be driven -- a lot of this is going to be

driven by dose reduction.

And it certainly seems to me that this is a question, as Dr. Smith said, not to be paternalistic, but this is why radiologists -- this why God made radiologists, to give value added to the studies that we are asked to perform.

And I think this is a clinical judgment question about whether FFDM is more appropriate for a particular patient, or the 3Ds. But I do think that eventually synthetic images are -- well, synthetic images seem to be taking over the world. But this is new technology, and it seems to me that practices will adapt to it.

DR. PAYNE: Tom Payne.

This is just directed at the FDA. It's just points to ponder, I assume, and that is, okay, the 3Ds process, if approved, when approved, will then negate doing the full-field digital. In other words, that wouldn't be done. And so the synthesized 2D image will -- the C-View will substitute, essentially, for the full-field digital.

So my comment is then, in the MQSA process, I'm assuming that a site will submit for approval or verification that the system is working, they'll present C-View images to be approved by accrediting bodies.

What's interesting, and it may or may not happen, but the device itself, the Dimensions machine, can obviously do both. It can do regular full-field digital images, and it can do the 3D images and then synthesize an image.

Potentially, the synthesized image, the C-View, might not need criteria, but the device itself in the full-field digital mode is just fine. Mainly, is there something -- you know, I'm not going to try and decide how Hologic has all the bells and whistles controlled by little widget controllers, but it's just something to -- the FDA has to ponder this, and the accrediting bodies will deal with it appropriately as from FDA direction. But I am just commenting that that's going to be a practical reality once this is set forward.

DR. ROSENBERG: Dr. Hooley.

DR. HOOLEY: Regina Hooley.

I have a question for Hologic. This is a question regarding comparison films, and it was actually brought up prior to the meeting, through e-mails by the Panel, and I don't think it has been fully addressed.

Are the C-View images able to be viewed on a non-Hologic workstation? So, for example, if a patient has the C-View study one year, then the following year moves or goes somewhere else, to a facility that only has 2D FFDM, will those prior films be able to be compared? I realize that we may not have a direct comparison because it's different technologies, but will the radiologist be able to see it, hopefully, optimally on a different vendor's workstation?

DR. ROSENBERG: Yeah, can they be exported or printed?

DR. LEVINE: The answer is yes. They're stored in the same DICOM MG format, so they would be able to be viewed on a PACS

workstation, as long as that PACS workstation was compatible with displaying mammography images.

DR. KRUPINSKI: And is the little C-View tag part of the metadata, so it would always appear with that C-View labeling no matter what system it's going to be done on?

DR. LEVINE: It's not part of the metadata. It's burned into the image. So yes, it would appear on any workstation.

DR. ROSENBERG: Dr. Dodd.

DR. DODD: Hi. Lori Dodd.

I have to come back to this issue of bias. It's sort of nagging me. And I guess I want to ask the FDA if they could be a bit more specific about what the specific bias concerns are with regards to this study and the non-inferiority design. I think that the concern in non-inferiority trials is that the comparison arm may perform worse than it would in practice.

So one question is, were there comparisons of the AUCs from this study and existing studies that have looked at the areas under the curve for full-field digital mammography, such as the DMIST study or the previous study submitted by Hologic?

If this looked considerably lower, there would be concern. I haven't seen any indication of that.

Another potential analysis would be looking at subgroups, which there were studies that were looking at various subgroups, and those

too seem to be robust to suggestions of bias. The only suggestion of bias was a very extreme case, which I actually don't fully understand. I could go back to those slides, but I won't take everybody's time here because I do think it's an extreme case, and I think we should discount somewhat for that. But that was the case where we assume missing at random in the 2D setting and non-ignorable missingness in the 3Ds setting. And that was the only case in which we were shown the actual decrease in the area under the curve for the 3Ds.

So the only other things I can think about are if there were some missing subgroups. So I don't know, architectural distortions. I don't know, is there -- there was a calcification subgroup. Invasive carcinomas. It would be helpful to get some input from the FDA, if there were specific subgroup analyses that you think might have suggested a difference in the opposite direction. And then also to the Panel members for their input.

DR. OCHS: This is Robert Ochs.

This reflects a little bit of a timing issue. So some of the issues that we initially identified and put into the Executive Summary we've since investigated. So initially it started out as what are your concerns? But in the interim time we found these robustness analyses, so now it's a little bit more of a general question of, you know, we identified some concerns and we did some robustness analyses. Is there anything else we're just not thinking of that you're really concerned about?

So there are no specific concerns per se, other than what we've presented and tried to analyze for the Panel, if that helps.

DR. DODD: Thank you.

So I guess the question to the Panel -- and maybe we can bring this up later -- is what other subgroups would one want to look at?

DR. ROSENBERG: Any thoughts from the radiologists about subgroups being both cancer and non-cancer cases?

DR. FAULK: Dr. Faulk.

Maybe just one quick comment on that. I guess I would look at those things where 2D is likely to be more beneficial than 3D, so the four things that were mentioned by Dr. Rafferty, I think, as well as the addition of developing densities. So the two big ones I would see would be asymmetric opacities and developing densities. They would be the two that I would have major concerns of that I don't think were probably addressed in this study.

And granted they don't comprise the majority of cancers, but they're not necessarily an insignificant number. If you put asymmetric opacities and developing densities, you're probably maybe somewhere in the area of 5% of all cancers, 3% to 5% of all cancers.

DR. ROSENBERG: Other questions from the Panel? Other discussion issues?

(No response.)

DR. ROSENBERG: All right. We're moving early. So it's now --

we'll call it 12:00, and I think we'll break for lunch. Okay, so we will break now for lunch, and we will reconvene again at 1:00 p.m. for the Open Public Hearing.

Panel members, please do not discuss the meeting topic during lunch amongst yourselves or with any member of the audience. And please take any personal belongings with you at this time. The room will be secured by FDA staff during lunch, and you will not be allowed back into the room until we reconvene.

Thank you, everyone.

(Whereupon, at 11:57 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:12 p.m.)

DR. ROSENBERG: Okay. It is now -- I have 1:11. And I would like to resume this panel meeting.

We will now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.

Ms. Craig will now read the Open Public Hearing Disclosure Process Statement.

MS. CRAIG: 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 you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group'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 such 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.

DR. ROSENBERG: Do we have any public speakers here today? I do not see or have heard of any that have registered. Are we missing anybody's -- missing anyone?

(No response.)

DR. ROSENBERG: Okay.

I guess I can go over the process to ensure a smooth transition for one speaker to the next, but that does seem to miss the point.

(Laughter.)

DR. ROSENBERG: Or miss the reality.

Okay. Hearing no objections, I would like to thank the Open Pubic speakers, of which we had none. Actually, I really would like to thank the Open Public speakers.

(Laughter.)

DR. ROSENBERG: And no one on the Panel can have questions, so I now pronounce the Open Public Hearing to be officially closed.

We will proceed with the remainder of today's agenda. All right.

We now return to the Panel Deliberations. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair.

Additionally, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers.

During the next hour, we will open up the floor to questions for both the Sponsor and the FDA. Okay.

Panel, we need questions to be answered, questions for the Sponsor or the FDA concerning what we've heard already.

Yes, Ms. George.

MS. GEORGE: This is Elisabeth George.

One of the questions I had is I've heard, a number of times, questions regarding the design of the study being different than other -- the previous study. I guess I'd like to understand, is it really that they were different, the content and makeup, and different just from Hologic's previous PMA or different in general across the modalities for mammography testing?

DR. CHEN: Weijie Chen from the FDA.

The study design paradigm, which is a controlled retrospective multi-reader, multi-case study with ROC methodology, this paradigm is the same as the study previously approved, the PMA study.

The difference that the Sponsor studied in their submission -- in my presentation, is the case mix, the relative proportion of the different categories, you know, benign, recall, and negatives. And the Sponsor stated that they reduced the number of cases in the recall category to reduce the

potential bias in favor of the new modality, 3Ds, okay, because most of the recall cases are from FFDM.

Another thing the Sponsor stated is that they increased the number of cases in the cancer category to gain statistical power.

Those are the two differences in case mix compared with the previous study.

DR. DODD: Can I follow up?

DR. ROSENBERG: Dr. Dodd.

DR. DODD: And just to verify that your re-analyses show that that case mix did not matter, correct?

DR. CHEN: Yes. The robustness analysis, we did show that it is not an issue.

DR. ROSENBERG: Dr. Dodd.

DR. DODD: That was my question.

DR. ROSENBERG: Okay.

So I guess I have a question, in part, for the Panel radiologists, and we may have it to the Sponsor and the FDA. It's a restatement of my prior question.

We, as radiologist-mammographers, routinely read with comparisons, probably 90% of the time. And this study, for a variety of reasons, mostly logistic and in parallel with prior similar studies, was done without comparisons. Is there any reason to believe that that would have

changed the results?

We may have to think about that for a second.

Dr. Faulk.

DR. FAULK: Well, maybe I'll start out by answering that just by rephrasing: Is there any reason to disbelieve it?

And I guess then it becomes a question, in my mind, of, I think, what we were wrestling with earlier in the conversation was: There is really no direct comparison or data available for comparing C-View versus conventional 2D FFDM.

So I'm wrestling with how do -- the same as you are, I think -- how do we answer that question, then, if 90% of what we do is comparison, what do we have to fall back on to answer the question? Could it make a significant difference to the results?

DR. ROSENBERG: In a differential? Yeah.

DR. FAULK: Yes.

DR. HOOLEY: I think that reading without comparison film is actually more difficult, which is why we always want those comparison films. Having said that, in the way the study was designed, neither are the 2D FFD comparisons as neither the 3Ds. So maybe that would eliminate the advantage of the comparison films.

We don't know, for sure, if comparing the 3Ds with 2D is going to be as useful as comparing 2D directly to 2D, but it seems that they are --

from what I've gathered, from the information that I've heard, that they are reasonably comparable and there are always differences in technique when we compare -- you know, as technology improves, certainly a mammogram done today, even just a 2D FFD compared to an analog film, there's a slight difference in comparison, or comparing one vendor's current 2D FFM with another's, there is a slight difference.

So I think we're sort of used to accepting some differences, and I hope, I don't know for sure, that maybe these differences will be similar.

DR. ROSENBERG: I think that's the question, but I think we just need to raise it and talk about it. Anybody?

(No response.)

DR. ROSENBERG: All right.

Please, Dr. Faulk.

DR. FAULK: Can I go back to one -- Dr. Faulk.

A question for the FDA.

DR. ROSENBERG: Yes.

DR. FAULK: And it was kind of brought up before, but I'm not sure I have a clear answer on it. Does the FDA and MQSA already have a way, in their mind, to deal with C-View in terms of MQSA?

DR. ROSENBERG: Ms. Morris, would you address that?

DR. FAULK: Do we know how that will be handled or --

DR. ROSENBERG: Is that our purview here?

MS. MORRIS: Well, it's somewhat not in our purview to talk about MQSA, but we have been working with the folks in MQSA. Dr. Barr is the head of MQSA, and so she's worked in conjunction with us. And if she's in -- so if she has a comment, I'd welcome her to come up.

DR. ROSENBERG: I guess that's two questions. Yes. You're in the audience and you're --

(Laughter.)

DR. BARR: It's Helen Barr, FDA.

Yes, we have been working closely together and with the accreditation bodies.

If this is not the only unit at a facility, then we would continue with the certificate extension program because nobody is yet ready to accredit 3D.

The question that we're going to be struggling with and working with the ABs, the accrediting bodies, on is if this is the only unit, do we have enough information from the 2D to accredit on the 2D and then use the certificate extension program for the 3D? And I don't have the answer to that yet.

DR. ROSENBERG: Thank you.

I guess Ms. Butler is here, but that wouldn't be useful, accrediting body.

Okay. Seeing no further discussions, we can now -- oh, yes.

Dr. Payne.

DR. PAYNE: Just on the same vein, I think Robert Faulk addressed this earlier, but I guess I'd like to just bring it and give it a little more light, and that has to do with if it is approved, there will be a label.

What is the FDA going to indicate that -- for the excluded situations, will those be excluded in the label and then what kind of liability does that throw on my clinical colleagues here, namely -- I think it's the prior biopsy, I think, would be the one. If that's put into the label, that that's -- the device was approved with that not being a part of the study; that could be an interesting thing.

I think the large -- I mean, a breast larger than the imaging system that's capable, I don't see that that would be an issue, but anyway.

MS. MORRIS: So it was mentioned earlier, by Dr. Ochs, that you always have the practice of medicine, and we don't regulate the practice of medicine. So we may clear or approve a medical device with explicit labeling, but that doesn't prohibit a practitioner to use his or her own judgment on how to use that device.

DR. ROSENBERG: Yeah. And probably a quick question for Dr. Rafferty, and that would just be are there particular surgical artifacts specially related to clips and things that wouldn't require specific training or interfere with the interpretation of the 3Ds images?

DR. RAFFERTY: Betty Rafferty.

I showed you an image that contained some surgical clips. I used that one because they're larger than most of the clips that we place at biopsy and cause more potential artifact. We've not found those to be problematic in clinical use of tomo. Obviously, we don't have C-View, but you can see that the artifact that they generate is minimal on the C-View image.

There also was the question raised about larger metallic objects such as a port or a pacemaker. We actually, if you'd like to see, have an image of a port on a C-View. It looks much as you would expect it to look, just a metallic object. But the rest of the image is appropriately reconstructed around it.

If that answers your question.

DR. SIMON: Can I ask a question? Again, to Dr. Rafferty.

I'm not a mammographer. But, I mean, there were patients that were excluded or exempted from the study, but it was really just for the purposes of doing a study. I mean, can you think of any patient, going forward, in a hospital or an institution that has this equipment installed, that should be excluded from a 3Ds exam? I mean, not necessarily based on the study, but is there any reason why a patient should not have a 3Ds exam? Is there any condition that you can come up with that, if you were writing the labeling, that you would say this group of patients should not get it?

Because otherwise, although the study had these exclusions -- and I don't want to open a can of worms -- I would actually say you don't

want the FDA really getting deeply involved in the labeling and saying patients should be excluded or these conditions should be excluded. I mean, it should really be left to the discretion of the doctor or whoever is controlling or running the exam. That individual should be the one.

You know, I'm not a mammographer, so it won't affect my daily practice, but I would just think you don't want the FDA meddling or -- I shouldn't use the word meddling, but getting into this level --

(Laughter.)

DR. SIMON: -- of detail. But, you know, I'm not a mammographer, so what should be excluded, if anything?

DR. ROSENBERG: Let me rephrase: In your clinical experience, are there any cases in which you have found artifacts or other problems with either tomosynthesis or specifically the --

DR. SIMON: Preexisting conditions.

DR. ROSENBERG: -- synthesized images?

DR. RAFFERTY: There is only one situation in which I have found that to be true, and that's the performance of a needle localization, because with the tomosynthesis reconstruction, the fenestration paddle, you're not able to see to the top of the paddle adequately to appreciate the alphanumeric grid. And so when I do a needle localization utilizing tomosynthesis, I always do it in combo mode, and so I use the standard 2D FFDM to see the alphanumeric grid. But that is the only situation that I can

think of.

DR. SIMON: Well, that answers my question.

DR. ROSENBERG: And will there be any other sites, clinical experiences, will be queried in this particular question?

DR. RAFFERTY: Right.

DR. ROSENBERG: In terms of training and --

DR. RAFFERTY: Right. This issue about the needle localization comes up a lot, but I've heard no other situation in which the tomo has been suboptimal.

DR. SIMON: Right. So with regard to labeling, I mean, that would meet my criteria for -- you know, for a preexisting condition. Or the way --

DR. ROSENBERG: Yeah. Dr. Faulk.

DR. FAULK: Yeah, a question. Dr. Faulk.

So I understand the labeling, but -- and that we don't want the FDA to put undue restrictions on us as physicians, but I think the point that I would have is normally, when we practice medicine, we're supposed to do it on the best scientific evidence available.

And the question mark is, do we have the best scientific evidence available to do it on women with implants or women with large breasts or women with tissue markers? Do we have that evidence? And if we don't and you do it, I understand I can still do it, but (a) do I have any good

scientific rationale to do it, and (b) is if I have an adverse outcome in one of those patients, what is my defense?

DR. WATSON: Along the same lines. I pretty much agree with what you said. And I don't think it's really -- I don't think we have the data to say we exclude that you do it in this patient or not, but what we can say is they have shown the benefits in this patient population, and it's narrowly defined as clinical trials and that's what we can say.

DR. KRUPINSKI: And just to verify. I mean, the labeling is not saying don't use it in these patients. It's simply saying what you said, is we don't have the scientific evidence and that it's up to the practitioner to take that into mind. So I don't think it's restricting anything. It's not saying don't use it on these patients; it's just saying we don't have that information; it's up to you.

DR. FAULK: Dr. Faulk.

I understand that it's not restrictive, but it is in the sense of the practice of medicine and the legal, potential legal, ramifications. There it has significant potential legal ramifications because you know, if you practice, that you can tell that to women, but there will be some women who have read whatever and want to have that done, and so then you've got a choice of either refuse them or do it. And, again, if you have the adverse outcome, you really don't have any scientific data to fall back on.

DR. WATSON: This is Karol Watson.

I think you are legally at risk either way, if you over-interpret the data or you under-interpret it. So what you can do is say what the data shows and this is what we would approve it for.

DR. ROSENBERG: And I also would guess that if you have funny artifacts, you would note it at the time and have the opportunity to do conventional imaging. So I suppose, in clinical practice, there's probably always another option.

Okay, let's go to FDA questions. We're moving ahead.

At this time, let us focus our discussion on the FDA questions. Copies of those questions are in your folders.

I want to remind the Panel that this is a deliberation period among the Panel members only. Our task at hand is to answer the FDA questions based on the data in the panel packs, presentations we heard this morning, and the expertise around the table.

With this said, I would ask that each Panel member identify him or herself each time he or she speaks to facilitate the description.

Please show us the first question. And then I'll make a comment after the first question. We'll take a break and then come back.

(Pause.)

DR. ROSENBERG: All right. Oh, good.

DR. OCHS: Okay. This is Robert Ochs.

Discussion Question Number 1: Hologic is proposing a new

screening option that does not include the acquisition of standard of care FFDM images. Please discuss aspects of performing and interpreting mammography that should be considered in the training and/or labeling when FFDM images are not acquired during the screening exam.

DR. ROSENBERG: Okay. Dr. --

DR. HOOLEY: It's Dr. Hooley.

DR. ROSENBERG: Oh, thank you.

DR. HOOLEY: It's all right.

I suppose it should be noted, as we've already discussed in depth, that there are no direct comparisons between the synthesized views and the 2D FFDM, and that of course you cannot directly compare the synthesized views with a 2D without the use of a tomo because it might be -- from what I've seen on the images, it might be easy for radiologists who are not well informed to want to compare the synthesized images with a 2D FFM, so it has to be very clear that they need to be looked at in combination with the tomosynthesis views.

And I don't know how you go about making sure that that's always done, whether it's just education and trust that they'll always do that or whether the images should always come out together when they're exported, perhaps, to another workstation, if the patients moves or goes to a facility that may not have the experience with the 3Ds. And that's something that should be considered.

DR. KRUPINSKI: Elizabeth Krupinski.

I think, just to reiterate, that the training part, that has to be especially directed towards those exclusion cases, and that's not only for the mammographer, but also for the techs who potentially are going to be making these decisions about which patients are going to be put into which imaging modality.

DR. FAULK: I believe somehow it would have to be addressed that if a woman had the 3Ds and then went to another facility where perhaps they only did 2D FFM, that there was somehow to address the situation of comparing a synthetic C-View image with a previous FFDM, because we don't really know what the comparison is between a C-View image and a conventional 2D FFDM. So somehow there may have to be -- addressing that situation.

DR. ROSENBERG: You're suggesting training, labeling?

DR. FAULK: Well, obviously training would be great, but that may not be totally feasible at the beginning, because usually that takes hundreds of cases, not a case or two. So I would imagine, initially, it would have to be labeling.

DR. ROSENBERG: And -- yeah.

MS. GEORGE: The question I have on that is, is that how do you train somebody who doesn't have the product that you're talking about?

But secondly, I guess, for the clinical people at the table, is how

many patients actually remember to even collect and bring historical images with them to their next practice?

DR. ROSENBERG: In my experience, they don't have to remember because the people who schedule them and take the mammograms ask.

DR. HOOLEY: We're pretty aggressive in getting prior films. Our technologists do it, our staff does it, so I would say we probably get it over 50% of the time, the prior films, maybe 75% of the time. We're fairly aggressive. And it's automatic in my practice.

DR. COLDWELL: Coldwell.

It seems to me that this could be easily solved by if you just put a label on the disc if you're going to export the images, that it would not -- done head-to-head comparison between C-View and traditional 2D FFDM and it's not been shown to be -- been no data shown about that and just put that on the CD and have it pop up on the computer when you load the disc.

MS. GEORGE: Is there a similar comparison between other modes of mammography that you would expect to see on discs, as well? So for MR, do you have that? I mean, what do you do to ensure that, as a clinician, when you have many different modes of imaging that you're looking at, that you're able to do those comparisons?

DR. COLDWELL: Coldwell again.

I think what we're dealing with here is brand new technology

and that it's not widely, obviously widely, dispersed yet; obviously, because it's not approved, but that it's going to take time to get widely dispersed and certainly into training programs where most people receive training in MRCT and other modalities. So it's going to take some time. And I think that until that time, everybody has to at least be made aware of the lack of comparison.

DR. HOOLEY: It's Dr. Hooley again.

We may not have a directly comparable situation with new technology, but we certainly see it all the time in our practice when we compare different methods of obtaining a breast MRI from an outside facility when it comes to us.

And sometimes we can't see every image the way it was interpreted at the original facility, but we do the best we can, and we just say images were obtained at another facility and they might use different sequences and different protocols than we do, but we do the best we can, and we just say we do it the best we can.

DR. ROSENBERG: Other thoughts, comments?

Dr. Payne.

DR. PAYNE: Just another comment with regard to training, and this I would address to the FDA.

In C-View, you know, we've defined it here. It's a synthesized 2D image from 3D images in a maximum intensity projection, a MIP-type thing.

The question, now, would be -- so I would say, in the training part, I think -- I'm sure you're planning to have adequate information, but I would reinforce that, that I think it's both the technologists that are going to be doing this, as well as the interpreting radiologist and also the medical physicist, that you provide some reasonable information as to exactly how this C-View is obtained so that they feel comfortable in knowing that. So that's one part of the training.

Then the other part, I guess, is more of a labeling question. In other words, for images that go off site, fine, it says C-View, but another radiologist -- I'm not thinking of an internist or the general public, themselves, but another radiologist sees C-View and goes -- and, you know, in outback Montana or something and does that person need to know that this is -- should there be some other asterisk or something in the DICOM header that alludes to the fact that this is not really a 2D full-field digital image?

That's just my comment.

DR. ROSENBERG: Okay. So I'll summarize on the Panel consensus, that there will need to be specific training for the technologists and the radiologists in reference to the differences. There will be issues related to use of C-View by radiologists outside the facility that has C-View. I think the consensus is that it may not be much different, but we don't really know, then these other changing technologies, whether it goes to film screen digital, different vendors, different MRs, that radiologists have this problem

and will have to do the best they can with interpreting new technologies from other facilities.

That was a long summary. Panel, any clarifications to that?

DR. PAYNE: In your inclusion of technologists, radiologists, please also add medical physicists. We don't want to be totally left out because we're going to be in there at some point, so might as well put us in now.

DR. ROSENBERG: So, Ms. Morris, yes. The medical physicists will actually need specific training, also, in evaluating these devices.

So the Panel generally believes that this is not an impediment but is a significant training issue and labeling issue, so that the other users of this system are fully aware of this not being a standard full-field digital image even though it looks very much like one.

MS. MORRIS: Thank you. You have answered Question 1.

DR. ROSENBERG: So we're going to take a 15-minute break. And we will adjourn now. It's 1:45, so come back at two o'clock to Question Number 2.

Thank you.

(Off the record.)

(On the record.)

DR. ROSENBERG: Ready? Is everybody in -- yeah, good.

Question Number 2.

DR. OCHS: Okay. Robert Ochs.

Does the panel have concerns with specific sources of potential bias, such as the case distribution, missing follow-up cases, and exclusions? Does the panel believe the presented analysis of these biases is sufficient?

DR. ROSENBERG: Please.

DR. DODD: I'll start. Lori Dodd.

So, first, I just want to express a frustration. I felt like the FDA presentation was a bit inconsistent, that there was some mention of bias, concerns about bias, but at the end, when the sensitivity analyses were presented, it appeared as if the bias wasn't a concern and it was -- I just wish that the presentation had been a bit more consistent throughout.

That said, I think the bottom line for the subset analyses and the sensitivity analyses indicate that for those cases considered, there is not much concern about bias, but I do think, based on the comments from Dr. Faulk, that there may be some specific subsets for which there remain concerns. And I'd like input from maybe Dr. Faulk and others on those specific subsets that were not examined.

DR. ROSENBERG: You're on.

DR. FAULK: Okay, yeah.

Significant issue for me. Again, I think, for me, it's the exclusions within the study that I'm wrestling with because there are large subsets of women that weren't included in this study, so again, the women

with the implants, the excisional biopsies, the tissue markers, large breasts. Then you've also got the situation -- we didn't look at the aspect of how does comparison with prior studies actually affect the endpoints of the study.

I think my question, which I directed to the FDA, was based on the study performed and the study population and the exclusions, and without a lack of comparison, is it reasonable? Are there any objective ways that we can reasonably or confidently be certain that the results of this study are transferable to the general population?

And I have some real concerns with that because if you take all of those exceptions, you're probably looking at 30% of the general population. If you look at the fact that the study was not done with comparisons, in most of our clinical practice, that's 90% of the patients. So I think there are a lot of uncertainties there, and I'm looking for a way to justify that I can have confidence that the results of this study are transferable to the general population with the endpoints that were done.

DR. ROSENBERG: Other comments from the radiologists, particular subsets, or I can ask you or others that you're concerned about?

DR. HOOLEY: It's Dr. Hooley.

It appears to me -- I don't see that large-breasted women would pose a problem with a 3Ds. It's just a different part of the breast that wasn't tiled and imaged. So I don't see that as being a worrisome exclusion.

Likewise, biopsy clips may not be a worrisome exclusion,

although I haven't -- I only saw some images, and I wasn't able to see them closely, that Dr. Rafferty showed, of the patients with biopsy clips on the 3Ds. On the tomo views, biopsy clips give an accordion artifact, and I assume, but I might be assuming incorrectly, that perhaps the 3Ds images take some of that accordion artifact out because it's only on maybe one or two slices and so perhaps, when they do the MIP, it is smart enough -- the program, the computer program, is smart enough to eliminate that. If that is the case, then I don't think that biopsy clips would be a significant impediment to the 3Ds.

Likewise, perhaps implants would not be, also. We haven't been doing implants with the tomosynthesis because of the increased radiation dose because these patients are already getting eight standard views. Implant cases are always difficult to read because there are so many pictures and the presence of the implants are there. But as long as there's no direct artifact related to the implants, I don't see that as being an impediment, although we have not seen images closely.

So maybe Dr. Rafferty can address what those images actually look like and if there is any significant artifact.

DR. ROSENBERG: Silicone injections, I assume, would be a real issue. These are rare, but we still do see them on occasion.

DR. HOOLEY: But that's always an issue even on a 2D FFM. I mean --

DR. ROSENBERG: Yeah. Dr. Rafferty, do you want to make

comments about clip artifacts and the need for at least additional training or at least information for the FDA in reference to clarifying that they're not a problem?

DR. RAFFERTY: Betty Rafferty.

You're absolutely right that the clips on tomo leave that slinky, I call it, or accordion artifact. That is resolved because exactly it's a MIP image, so I showed you -- I know that I didn't show you many images. It was kind of to try and address this issue that clearly had come up that I wanted to include some cases that we had. We do image the patients with implants at Mass General using combo. We choose to do it only in the implant-displaced view to try and minimize the number of images. There are no guidelines here. That's why I think that this is an important technology for certain subpopulations, because it really does allow them to avail themselves of the tomosynthesis at a more reasonable radiation dose.

In terms of other artifacts, we have not noticed any problems with implants or with clips. As I said, the only thing I've noticed a problem with is the fenestrated needle causation paddle, itself.

DR. HOOLEY: I suppose there might be a rare instance, and this would be very rare, where you might see a suspicious lesion only on the 3Ds, in which case you may have to try to localize it either without using the 3Ds or using the 3Ds with the artifact. I think that would be an unusual scenario, but I think it's possible.

DR. RAFFERTY: Shall I comment to that?

DR. ROSENBERG: Please.

DR. RAFFERTY: I mean, you can see worrisome lesions on the 3Ds alone, sometimes. The question, the first question, is are they real? The majority of the time, they too are summation artifact from the images. It's quite remarkable, sometimes, how similar those two things look. The *n* is small, but I haven't seen a case where there's something worrisome on the 3Ds that is not reproduced from the tomo.

DR. HOOLEY: One more comment. I suppose it will just take time, when you do follow-up exams, to know that perhaps you did have a false negative based on a suspicious finding on a 3Ds.

DR. RAFFERTY: That's absolutely true.

DR. ROSENBERG: And there were cancers that were dismissed on the 3D. Do you have any comment about those?

DR. RAFFERTY: Yes. I mean, within the entire distribution, some patients undoubtedly dismissed cancers on the 3D, and I don't have any specific comment about that. That's kind of what the training is really focused on, is analyzing that and making appropriate clinical decisions based on that.

And I'm sorry, Dr. Rosenberg. To your point with respect to training in terms of these artifacts, I think that these are things that can be incorporated into the tomo training fairly easily. We already have some

examples of similar things in the current tomo training, and then that could just be enhanced.

DR. FAULK: Dr. Faulk.

You know, I really appreciate the anecdotal -- you know, from people who are actually using DBT, that's really helpful. But it would still raise the question in my mind, does anecdotal evidence justify extrapolating the results of the study to the general population?

DR. DODD: Lori Dodd.

I just want to come back to the bias issue. I've learned that if I don't ask even the dumbest questions, I regret it later.

What about these other features? So tumor size, architectural distortion, asymmetric density, I don't know all the right terminology for these things, but I know those are some features that are looked at that were not looked at specifically here. How much does the lack of information specific to these features concern you?

DR. ROSENBERG: I would guess the one that isn't addressed is developing densities or developing focal asymmetries, if we're going to be proper.

DR. FAULK: Dr. Faulk.

Perhaps asymmetric capacities, too, because with asymmetric capacities, it's usually helpful to have the comparison mammogram. Yeah.

DR. ROSENBERG: Dr. Hooley, comments on --

DR. HOOLEY: I think we have different terminologies. The focal asymmetries that we see that are developing, it's a relatively uncommon presentation for a cancer. I would say that's one of the least common presentations for cancer, so since we don't know whether it's helpful or not, because we didn't have the comparison uses to analyze this -- however, we do know that, as far as spiculated masses goes, it seems that the tunnel in the 3Ds does perform better, which I think is important because that's the more common scenario, and those are the more worrisome types of cancer because they're usually in basic cancers.

DR. ROSENBERG: Dr. Smith, any other comments on --

DR. J. SMITH: Pardon me. I'm Justin Smith.

You know, I was wondering about -- although it may not be dead onto this question, but I hear them talk about the biases and the subgroups of individual patients that may not have been addressed, that weren't addressed. You know, I just wonder, if the recommendation is to approve, is there a role for a Phase IV post-market surveillance component?

And I don't even know if that's part of our purview, but it just seems to me that given this lingering sense of "are we missing something" and I mean the possibility because these groups haven't been studied, is there a role for that kind of a requirement potentially?

DR. ROSENBERG: Ms. Morris.

MS. MORRIS: So maybe it would help if I kind of outlined some

of our tools that we use for regulatory decision making.

So the premarket decision is whether or not the dataset presents sufficient evidence for a reasonable assurance of safety and effectiveness. And many times you make the decision that there are exclusions, but it's generalizable and you can include them. Other times, you would say you cannot and you need to exclude them from the indications for use.

There are other situations where both there is, like, a more long-term unanswered question, the immediate question for one group of patients where there is a reasonable assurance of safety and effectiveness; you can proceed to go out on the market, but there is an outstanding question that the study could not address. Then we would consider post-approval studies.

But you run the risk of being too -- you have to be very specific about your question; otherwise it turns out not to be a highly useful endeavor. Either you can't recruit patients or it's not well-defined, in which case you're not answering the question and it becomes kind of a waste.

So we do have post-approval study requirements, we have labeling requirements, where if you felt that these exclusions should not be part of the indications for use, the sponsor could come back at a later time with a supplement with new data to include them and then expand the indication, just like they've expanded this indication from their original

approval.

DR. J. SMITH: Justin Smith again. Thank you.

I am tossing out for consideration, then -- I mean, given that we have a set of women that for whom the study is representative and those for whom it isn't representative, or at least we don't know that they're represented because they weren't included, would that be the sort of tool that the FDA could use to say "approved for the women that were studied" and then, in post-market, come back with a supplement for the women that were not studied?

By the way, I have been on the other side. Having run a start-up, I've been on the other side of this table, and I am very mindful about how I felt when someone suggested post-marketing studies, so I don't say it with --

(Laughter.)

DR. J. SMITH: Please.

DR. ROSENBERG: Ms. Morris.

MS. MORRIS: So I just want to separate the options and make sure I understand you.

So you can make one decision that you should exclude those patients, you know, from the approval of the device, and it's up to the sponsor to come back and request an expansion with new data. It doesn't require a post-market study. But if you felt to look at the overall safety and effectiveness, not for the initial group, but for whatever the question is

you're trying to answer and it's critical to public health, then you would be very specific and have a requirement. But you don't necessarily have to have those two combined.

DR. ROSENBERG: Okay, other --

DR. COLDWELL: This is Coldwell. Just one quick comment.

I think that these cases, that these segments or sub-segments that were excluded, provide ample opportunity for an ample encouragement for academic studies to be done and papers to be written and things like that, that probably the data will be gathered one way or another whether we require it or not.

So it seems almost superfluous, in some respects, to require it as a post-market study when we all, at this table, know that within the next few years, these sub-segments will be addressed and the results will be published.

DR. ROSENBERG: Okay, other comments?

(No response.)

DR. ROSENBERG: So, Ms. Morris, with regard to Question 2, the Panel believes generally that there are some elements that were not included in the trial, but it's not clear that any of them would have results significantly different from what the trial showed generally.

Would that be a good summary from the group? Is that an adequate answer?

MS. MORRIS: Yes.

DR. ROSENBERG: Okay. I think we're then up to Question 3.

DR. OCHS: Robert Ochs.

The study protocol excludes subjects with previous surgical (excisional) biopsy. Does the Panel have concerns with the generalizability of 3Ds to subjects with previous surgical (excisional) biopsy?

DR. ROSENBERG: So this is actually related to Question 2, but it's a very specific question.

Panel, any further thoughts on either -- I assume this would refer to either the clips or the post-surgical findings, which we probably should include, also. Lumpectomies, not just -- yeah. Post-therapy changes would probably be in this whole group.

Please, Dr. Faulk.

DR. FAULK: I guess I'll just reiterate. I don't think we really have any data to support or deny it one way or the other. I think it's an unknown at this point in time with the exception of anecdotal data of people who have been using DBT.

DR. ROSENBERG: Correct. And I assume that the reading radiologist's view, as example, could always repeat standard views if you had a specific question; there's always a backup?

Please.

DR. WATSON: This is Karol Watson.

It certainly seems to me that this is a patient population, prior occlusional biopsy, prior lumpectomy, that really would be very -- certainly, from an advocacy standpoint, came to know about and have access to this type of procedure, and I think exactly what you said is the right way to look at it. Clinicians will know whether they can stop here or go further, but I think to de facto deny that population seems wrong.

DR. ROSENBERG: Okay.

In reference to advocates, Marlena, any comments?

DR. VEGA: Well, being big-breasted -- no. I think that there's something here that -- I don't know if you want to call it good faith or -- I think, thank God, I'm here after three interesting bouts, that most people that I've come across have a conscience, and it's really an important thing to understand that the people like yourselves, who would be dealing, will ask important questions, will not shove people into categories just to shut them up or to -- you know, no matter how pesky, someone who says oh, I know what this is, I need -- I think what has happened is that sometimes we've come to mistrust a little bit too much some of the humanity that really does exist. And it goes a long way to have a cup of coffee and a little -- but something here, it's called a challah, and that's where my grandmother explained to me the ways of the world.

And it was really a very interesting piece because what it was, she did it in Yiddish and Spanish and being also black, it was not easy. What it

does is it really, really has you ventilating, talk about things that bother you. You then share that with somebody who will get that information to somebody, and lo and behold, when you walk into an office, people really are not there to say "next." They're really there when they see your concern. And judging from some of the people that I've seen today and I heard today, I must tell you, I'm leaving here rather inspired.

And usually I leave these things saying boy, next time, I'm not coming, it's too long, I have grandchildren, I'm not going to do -- but this time I'm leaving with hope. Not the air of hope, but really hope, because I really believe that everybody here is trying to help people to help themselves. And so that may not be advocacy in its truest form, but it is common sense, and since we have a Tom Payne on our board with common sense, would be relevant.

DR. ROSENBERG: Ms. Price, any comments?

MS. PRICE: Carol Price.

I have very mixed feelings over all of it. As a survivor, I don't want to see any new technology denied people to help them in further diagnosis. As somebody who's been involved on the medical side with research, I like to see the proof. I like to know that we're not going to do any harm, that we've covered all our bases, and we haven't -- with these studies, we have not covered all the bases. There are biases there that haven't been addressed, so I have concerns over that.

I have concerns over the labeling and the FDA's response of saying, you know, primary physicians would just be ordering mammography screening, and then the radiologists would be making the decision as to what type of screening they would get, when at the present date, that would not be happening because there are very few institutions at the moment offering 3D tomosynthesis. So if you have that facility in town, is your primary physician going to know that you're the person that needs to be sent to that facility instead of the normal facility he uses for screening purposes? So I have a lot of mixed feelings over the issue, so --

DR. ROSENBERG: Thank you.

Dr. Hooley.

DR. HOOLEY: Regarding radiologists making decisions on which medical imaging tests to perform, we do that every day in all modalities. We give advice to patients, referring physicians. We veto tests that aren't appropriate, and we tell people which tests they need. So it's part of our training, and we're used to having that discussion on multiple levels.

DR. ROSENBERG: Yeah, please.

MS. PRICE: Carol Price.

I understand that. I truly do. I'm just saying that the physician doesn't know that that exists within his city, okay. The radiologist wouldn't be able to inform him of it?

DR. HOOLEY: That's correct. If the physician doesn't refer to

the facility that may have a new technology, they may not be aware of it, but I think that's true with any new technology. And hopefully, if a new technology is successful, there will be increasing awareness among the medical community and the public, and so we move in the direction of pushing technology forward. And I think that would happen with any new technology, really.

DR. ROSENBERG: Dr. Smith.

DR. J. SMITH: If I could just quickly address. You mentioned, Ms. Price, that -- I know that in Seattle, Washington, if -- given the competition in our area, if one hospital got even a broom that was somehow technologically superior, believe me, the other hospital would have it in a heartbeat. And the women --

DR. HOOLEY: And there would be billboards all over town saying who had it.

(Laughter.)

DR. J. SMITH: And keep in mind that also, because I think you were kind of pointing out that, you know, in the land of Microsoft and Google and so on, Amazon, which is where I live, there is an extensive network. Patients will come to see me, and they're now like the detail people. They'll tell me about what my literature is showing, and it's both exciting and humbling, and I think that that's a good thing.

The problem that many of us also face is the increased pressure

to get the studies done. And so in some sense, and it's not by way of excuse, but just sharing the world, there is this conflict within the radiologic community -- or I should say at least some parts of it -- that you want to do as good as you could, say, 10 years ago; you had the time. Now you don't have as much time, yet patients have every right to the information, they have every right to understand the test and have their questions answered. That's the challenge. And trying to find the way to help, at the same time, for all of us to go home at a reasonable time, too.

DR. ROSENBERG: Dr. Dodd and Dr. Vega.

DR. DODD: Lori Dodd.

I just want to follow up on the comment, because I do agree with the concern that there is a potential for bias and that we have to make decisions based on the best evidence in front of us.

So I think, at least, what my take-home message is, does it seem reasonably likely that it's an improvement or that it's as good as 2D plus the 3D, yet -- well, 2D alone, excuse me. Yes.

Are there some specific populations or subpopulations that can be identified from the outset that it might not work as well in? Yes.

Are there some specific subtypes of cancers or lesions where it may not work as well in? We don't know.

And so I completely am sympathetic to the concern of there being a potential for bias, and we just have to keep that on the table. Does

that mean that it's not worth going forward with? And I think that we'll come to that when we vote.

DR. ROSENBERG: Yes.

DR. VEGA: Hi. I would just like to say something that's really important to everybody here because I can't go home and go to sleep tonight or at least look in the mirror and not say this.

I just came back from one of my vacations, which means that once a year I get in a bus, a mammography van, and I go around wherever. I teach the Macarena for self-exam. And this year I was in the Caribbean, and I just came back from Antigua, the islands, and there are no radiology -- there's nothing there. Once you're diagnosed, okay, you can go to another island if, in fact, you can find the island and you can pay for it, but the likelihood is that you can't.

So I met about 26 women who had been diagnosed with Stage -- from II to IV cancers, and they had just the opportunity just to have chemo, that was it. So I'd like to put everything into perspective, and say if we have more tools in our tool chest or our chest, wherever it is, then I think that that's a blessing.

DR. ROSENBERG: Dr. Faulk.

DR. FAULK: Dr. Faulk.

One question, one comment. A question for Dr. Rosenberg.

We were talking a little bit ago about, for these subsets of women, if you did a 3Ds study and it was deemed to be inadequate, either a QC or artifact, whatever, then you would do something else. Does that mean a callback, then?

DR. ROSENBERG: A technical callback, in my experience, is something we routinely do for motion or -- you know, positioning inadequacy. So I don't know that, in this situation, it would necessarily be different. The question would be, would there be something we might not recognize.

DR. FAULK: Yeah, I agree with that. But technically, in the definition, it would be a callback.

DR. ROSENBERG: Yeah, technically a callback.

DR. FAULK: So it would affect obviously the callback rate.

DR. ROSENBERG: I think -- well, it's an easier question. I think technical callbacks are its own subcategory, but --

DR. FAULK: Then the comment is that it is true, that as radiologists, we are trained and part of our job is to select the best test for patients. The difference in the rest of radiology is that generally, that's done with the ordering physician, and it's usually done on a much smaller volume, as usually in CT, MRI, ultrasound, nuclear medicine, which is a much different situation than seeing large volumes of women and going through the different options available to them in terms of breast imaging. I think they're

totally two different animals.

DR. ROSENBERG: Do you have anything, Dr. Smith?

(No audible response.)

DR. ROSENBERG: Okay. Any other comments, questions on 3?

(No response.)

DR. ROSENBERG: So in reference to Question 3, the Panel generally believes -- well, that women with previous biopsies would not need to be excluded, but as with other small subsets, we don't really have all the information that we wish we had, which is the way the system works.

We always would like another view; that would be the radiologists' mantra.

MS. MORRIS: But can I just restate, does the Panel have concerns about the generalizability of 3Ds? And to subjects with previous surgical biopsies?

So it sounded like no. You felt that it is generalizable, correct?

DR. ROSENBERG: Yeah, we think it is generalizable, but -- yes. Panel, is that reasonable? Yes.

Okay. Question Number 4, please.

DR. OCHS: Robert Ochs.

Please discuss any other concerns with respect to the safety, effectiveness, or benefit/risk associated with the proposed expansion to the indications for use.

DR. ROSENBERG: One second.

Specific questions, and Shanika was noting questions about generalizability.

Does anyone on the Panel have major questions on whether generalizable is a problem? Just yes/no, please.

We can just start out with Dr. Simon.

DR. SIMON: No, I do not have any questions about it.

DR. WATSON: Karol Watson.

Am I only allowed to say yes or no?

(Laughter.)

DR. WATSON: The answer is no.

DR. ROSENBERG: Comments are fine.

DR. WATSON: Then can I make one quick comment?

I think I agree with what Dr. Dodd was saying. We make decisions based on the incomplete evidence base all the time, and it comes out, whether or not the evidence you have supports more or less generalizability. And I think the answer is we have more evidence for generalizability than not.

DR. ROSENBERG: In other words, than our usual information.

DR. SIMON: Can I make one statement here?

DR. ROSENBERG: Yeah, please.

DR. SIMON: On this issue of the specific Question 3 was

whether it was generalizable to surgical (excisional) biopsy patients. You know, sometimes patients are excluded from a study because their underlying condition may mask an effect, like they'll pull out patients who are on dialysis in certain studies. I think we're over-interpreting this.

This group of patients was pulled out not because we thought the modality would fail or in some way we wouldn't see this effect; it was merely pulled out because it would have meant changing the protocol of the study. So you would have needed to provide the radiologists with prior views.

So I think we're frankly over-debating this issue. It's not that we think it's going to fail in this group; it's just for the purposes of doing a study, you didn't want to provide old images. And I think that's simply -- and I think we can all, frankly -- and I'm not a mammographer -- generalize that it should work without any difficulty in this group of patients.

DR. ROSENBERG: I think it was simply an important subgroup. We just wanted to clarify.

DR. SIMON: I understand. But I think there's no reason to think it would fail in this subgroup.

DR. FAULK: Dr. Faulk.

Yes, I do have concerns that the exclusions limit the generalizability of the entire population and whether the results of this study are transferable to the general population.

DR. J. SMITH: I don't have strong feelings. I'd say no, I don't have them.

DR. KRUPINSKI: Elizabeth Krupinski.

No, I do not have significant concerns.

DR. PAYNE: Tom Payne.

I have no additional concerns or no additional comments.

DR. COLDWELL: Coldwell.

I have no additional concerns, and I think that it is generalizable.

DR. ZISKIN: Ziskin.

I do have concerns about how far you can go, and it's similar to what Dr. -- I'm sorry, I don't know your name -- Faulk has said.

DR. DODD: Lori Dodd.

I think I've already expressed my concerns about generalizability. I think, by reason, there may be some subpopulations -- maybe the excisional biopsies are not a concern, but for some other subpopulations, there may be a need for ongoing research.

DR. HOOLEY: Dr. Hooley.

I do not have major concerns regarding generalizability, but one comment I have about the exclusion of the excisional scars, I think that perhaps by excluding these patients, the specificity might have been biased and in favor with the 3Ds. However, I think these cases are relatively

uncommon; I would predict that, and so I don't think it would be significant, but I don't know for sure.

DR. ROSENBERG: Okay. So we need to modify a little bit my answer to Question 3, and that is there is a lack of unanimity that there may be some issues with this subset. In part, I think, if I'm not -- I'm speaking for the people who have a question, it was simply not tested, so we just don't know.

MS. MORRIS: Thank you, that's fine. We'll take that in advisement.

DR. ROSENBERG: All right, Dr. Ochs. One more time. Question 4.

DR. OCHS: Robert Ochs.

Please discuss any other concerns with respect to the safety, effectiveness, or benefit/risk associated with the proposed expansion to the indications for use.

DR. ROSENBERG: Let's just go around, if anyone has any other questions. We'll start with Dr. Simon.

DR. SIMON: I felt like everything was asked and answered previously.

DR. ROSENBERG: You've been in front of juries.

(Laughter.)

DR. WATSON: No additional questions or concerns.

DR. FAULK: No additional comments at this time.

Dr. Faulk.

DR. J. SMITH: Justin Smith.

No additional comments.

DR. KRUPINSKI: Elizabeth Krupinski.

No additional comments.

DR. PAYNE: Tom Payne.

I would just say I would actually go to the positive statement and say the fact that we can't approve something, or if it is approved, that way it would negate the full-field digital exam, the benefit/risk -- namely, the risk would go down. So I think it's moving in a positive direction in that arena, so I would say that's a good thing.

DR. COLDWELL: Coldwell.

No additional comments.

DR. ZISKIN: Ziskin.

I agree with Dr. Payne about this.

DR. DODD: Lori Dodd.

No additional comments.

DR. HOOLEY: Regina Hooley.

I have no additional concerns or comments.

MS. GEORGE: Elisabeth George.

No additional concerns or comments.

DR. VEGA: Nada.

(Laughter.)

MS. PRICE: Carol Price.

I just want to reiterate that it is going in a positive direction. As a consumer, we really appreciate that the radiation risk would be going down with this factor.

DR. ROSENBERG: Okay. In reference to Question 4, Ms. Morris, the Panel generally believes that there are no additional concerns that have not been addressed.

MS. MORRIS: Thank you.

DR. ROSENBERG: Is this adequate?

MS. MORRIS: Yes, it's adequate.

DR. ROSENBERG: Okay, we are ahead.

Okay. FDA and Sponsor summation time. At this time, the Panel will hear summations, comments, or clarifications from the FDA. You have 10 minutes.

MR. FRIEDMAN: My name is Arthur Friedman.

First of all, I'd like to say that C-View is the next step in tomosynthesis and mammography. And as said before, it's a tool or an option that's available to doctors and physicians that we believe will show superior results than 2D alone.

Hologic will continue to work with the FDA to address the

labeling concerns and the training concerns that were raised by the Panel. And we would like to thank the Panel for their guidance and their input.

Thank you.

DR. ROSENBERG: I guess that's backwards. FDA have any summation?

MS. MORRIS: No, we have no additional comments at this time.

(Laughter.)

DR. ROSENBERG: I mean, hearing that, I assume there were none, but -- okay, thank you.

Before we proceed to the vote, I would like to ask Carol Price, our Consumer Representative; Elisabeth George, our Industry Representative; and Marlena Vega, our Patient Representative, if they have any additional comments.

We'll start with Ms. Price.

MS. PRICE: No additional comments.

DR. VEGA: Another nada.

MS. GEORGE: Nothing additional, thank you.

DR. ROSENBERG: All right. Well, I would like to, on behalf of the Panel and the FDA, thank you very much for your time and participation in this discussion.

Voting instructions. Okay, we are now ready to vote on the

Panel's recommendations to FDA for this PMA. The Panel is expected to respond to three questions relating to safety, effectiveness, and risk versus benefit.

Ms. Craig will now read three definitions to assist the premarket approval application voting process.

MS. CRAIG: The Medical Device Amendments of the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert Advisory Panel on designated medical device pre-market approval applications -- PMAs -- that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in application or by applicable publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety, C.F.R. 21 Section 860.7(d)(1) - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risk.

Effectiveness - There is reasonable assurance that a device is

effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid Scientific Evidence - Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance for the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

DR. ROSENBERG: The Sponsor has proposed the following Indications for Use Statement: The Hologic Selenia Dimensions system generates digital mammographic images that can be used for screening and diagnosis of breast cancer. The Selenia Dimensions (2D or 3D) system is intended for use in the same clinical applications as a 2D mammography system for screening mammograms. Specifically, the Selenia Dimensions system can be used to acquire 2D digital mammograms and 3D

mammograms. Each view in a screening examination will consist of:

- a 2D image set, or
- a 2D and 3D image set, or
- a 3D image set in combination with a synthesized 2D image set.

The Selenia Dimensions system may also be used for additional diagnostic workup of the breast.

We will now proceed to the vote. Ms. Craig will read the voting procedure and the questions.

MS. CRAIG: Please locate your ballot sheets that have been placed inside of your gray folder and sign your name to the top of the ballot.

Please print your name on the ballot.

DR. ROSENBERG: Please. These are doctors.

(Pause.)

DR. ROSENBERG: We will pass them around. One per person.

(Pause.)

DR. ROSENBERG: Anyone else need a ballot?

MS. CRAIG: Question 1 reads as follows: Is there a reasonable assurance that the Selenia Dimensions 3D System with C-View software module is safe for the proposed indications? Please vote.

(Panel vote.)

MS. CRAIG: Question 2 reads as follows: Is there a reasonable

assurance that the Selenia Dimensions 3D System with C-View software module is effective for the proposed indications? Please vote.

(Panel vote.)

MS. CRAIG: Question 3 reads as follows: Do the benefits outweigh the risk of the Selenia Dimensions 3D System with C-View software module for the proposed indications? Please vote.

(Panel vote.)

MS. CRAIG: Panel members, please fold and pass your ballots forward. Everyone please give me a couple of minutes while we tally the vote.

(Pause.)

MS. CRAIG: The votes have now been captured.

On Question 1, the Panel voted 9 to 1 that the data shows that the Selenia Dimensions 3D System with C-View software module is safe for use in patients who meet the criteria specified in the proposed indications.

On Question 2, the Panel voted 9 to 1 that there is a reasonable assurance that the Selenia Dimensions 3D System with C-View software module is effective for use in patients who meet the criteria specified in the proposed indications.

On Question 3, the Panel voted 9 to 1 that the benefits of the Selenia Dimensions 3D System with C-View software module do outweigh the risks for use in patients who meet the criteria specified in the proposed

indications.

For the record:

Dr. Justin Smith voted yes for Question 1, yes to Question 2, and yes to Question 3.

Dr. Karol Watson voted yes for Question 1, yes for Question 2, and yes for Question 3.

Dr. Daniel Simon voted yes for Question 1, yes for Question 2, and yes for Question 3.

Dr. Robert Faulk voted no for Question 1, no for Question 2, and no for Question 3.

Dr. Elizabeth Krupinski voted yes for Question 1, yes for Question 2, yes for Question 3.

Dr. J. Thomas Payne voted yes for Question 1, yes for Question 2, yes for Question 3.

Dr. Marvin Ziskin voted yes for Question 1, yes for Question 2, yes for Question 3.

Dr. Douglas Coldwell voted yes for Question 1, yes for Question 2, yes for Question 3.

Dr. Regina Hooley voted yes for Question 1, yes for Question 2, yes for Question 3.

Dr. Lori Dodd voted yes for Question 1, yes for Question 2, and yes for Question 3.

DR. ROSENBERG: All right.

All right, before we conclude, are there any final comments from the Panel concerning the proceedings?

(No response.)

DR. ROSENBERG: The Panel was fabulous. I appreciate everyone's input. I appreciate the Sponsor, Hologic, and their presenters for clarifying what could be difficult questions.

And, Ms. Morris, do you have anything else to ask the Panel or say?

MS. MORRIS: Thank you very much.

DR. ROSENBERG: Okay, simple.

Okay, it is 3:06. The October 24th, 2012 meeting of the Radiologic Devices Panel is now adjourned. Thank you.

Thank you, everyone.

(Whereupon, at 3:06 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

RADIOLOGICAL DEVICES PANEL

October 24, 2012

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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ZACHARY DUNCAN

Official Reporter