So the sponsor asked: Is the rate of cancer detection for T-Scan positive women in the indicated group greater than the rate of cancer detected otherwise?

The table shows the relative probabilities for each of the T-Scan sensitivity values. The first data column, T-Scan specificity equals 94.7 percent -- that's a typo in the column heading on the slide. FDA's calculated relative probability for 26.4 percent sensitivity is 4.9, same as the sponsor's.

The relative probability declines with declining T-Scan sensitivity, down to 1.9, 1.0 and zero. Note that 1.0 and zero are at or less than one. A relative probability of 1 would occur if women were randomly selected from the intended use population to undergo further screening, and relative probability is less than 1 if the selected patients are less likely to have breast cancer than the overall T-Scanned population.

The right hand side of the table shows the relative probabilities for T-Scan specificity equals 88 percent, which had been found in the specificity

arm for African Americans and Hispanics. The relative probabilities are all lower and less than 1 when T-Scan sensitivity is 10.3 percent or less.

The logistic regression analysis shown to you in the statistical presentation showed that four variables are important to consider when doing a benefit analysis: Menopausal status; country; family history; and hormone use. Note that using T-Scan sensitivity for subgroups, like I just did, only accounted for country and family history.

There was another limitation to the sponsor's method, which has been mentioned earlier this morning. The intended use to screen women and then send the T-Scan positive women for further screening -- say for this discussion film mammography, which is currently the most frequently used technology and is an intermediate step. The intermediate step subjects the ultimate performance of T-Scan to the performance of the intermediate step.

The T-Scan sensitivity arm bypassed this intermediate step by testing women who were already scheduled for biopsy.

Turning now to the benefit/risk analysis, FDA based its method on the one used by Feig et al. in their study, which is referenced in your Panel pack. They showed this table of benefits and risks from annual screening mammography of 1 million women age 40-74.

They estimated that almost 19,000 lives would be saved at a cost of almost 22 deaths, for a net benefit of almost 18,900 lives.

FDA updated their calculation of deaths caused by using a lower radiation dose per mammographic view, and then adjusted the lifetime risk estimate to account for greater risk for women age 35. FDA calculated that there would be 14 deaths per million mammographic screens of women age 30-39. The number of deaths would depend on the number of women referred to mammography because they were T-Scan positive.

I'm sorry. I'm getting ahead of myself here. Rather than lives saved, FDA calculated cancers detected in 1 million T-Scanned women, which would be 1 million times the presenting prevalence of breast

cancer times the T-Scan sensitivity times the sensitivity of mammography.

I will now walk you through estimates for each of these factors, beginning with presenting prevalence. What is the prevalence of breast cancer among women who would present for T-Scan, which I am calling here the presenting prevalence?

First, FDA calculated the rate for all women age 30-39 from national SEER data. We used SEER data because screening populations tend to be enriched with high risk women and prevalent cancers. Using interpolation, which takes care of the small disturbance of the incidence curve at 35-45 (So in other words, if you expect screening starting at age 40 to catch cancers that were missed, you would expect that it would take into account ones missed between 35 and 39, and there is a small blip in the curve, goes down a little bit at 35-39, up a little bit at 40-44.)

So taking the average of prevalence at age 30 and incidence at each following year, resulting in the estimate of 0.058 percent for the presenting prevalence.

Then FDA calculated what the rate would be for those women in the age group who are also family history negative and clinical breast exam negative. For family history, FDA used data from a meta-analysis of 52 studies. This was also the source used by the sponsor. The proportion of women age less than 40 who are family history positive was estimated as four percent. The relative risk of cancer for these women was about 3.

For clinical breast exam status, FDA found only one study that addressed the rate of positive status and the associated relative risk. That study was by Bobo et al. and is referenced in your Panel pack.

The prevalence of clinical breast exam positive status was higher in women age 30-39 than among age 40-49. So because of FDA's concern that the estimates for age 30-39 were biased, FDA used the data for age 40-49. Those estimates were that 0.087 percent of women were clinical breast exam positive, with a relative risk of breast cancer equal to 25.

Since those estimates seemed extreme and

might also be biased, FDA also tried using 3 percent prevalence of clinical breast exam positive, and rate ratios of 10 or 3. These estimates produced calculations that were more favorable to the sponsor.

FDA derived the rates of cancer by family history and clinical breast exam status in 1 million women. FDA assumed that family history is not related to clinical breast exam results, so that there would be 40,000 women who are family history positive and 960,000 women who are family history negative.

This slide shows that, when the Bobo estimates were used, as shown in these top four data lines, the calculated rate of breast cancer in the 876,480 women who would be both family history negative and clinical breast exam negative would be 0.000174.

If we do the same thing assuming 3 percent prevalence of clinical breast exam positive associated with a relative risk of breast cancer of 3, then for the 931,200 women who would have both family history negative and clinical breast exam negative, their breast cancer prevalence rate would be 0.000507, which

is very close to the 0.00058 estimate for all women age 30-39 that we calculated from the SEER data.

Turning now to mammography sensitivity for women age 30-39, FDA found that the best estimates are for women in their forties. The sponsor estimated 70 percent, which was obtained from the literature, for older women. That is women over 40. FDA selected 50 percent from the Pisano estimate for film mammography for women age 40-49. This was based on one-year follow-up. The reference is in the Panel pack.

FDA noted that digital mammography found many more cancers than film in that age group, which explains the lower sensitivity estimate for film in that study. However, sensitivity decreases with younger age, as explained in the executive summary, even when post-menopausal women are excluded from the analysis.

To be conservative, FDA selected a 5 percent reduction from 50 percent to obtain 45 percent sensitivity for women age 30-39.

There's a lot on this slide. It shows the calculated net benefit for screening 1 million

intended use population women with T-Scan. Because the specificity is 94.7 percent and the number of true positive women who would be sent for mammography is small, each scenario says that about 53,000 women would be sent for mammography. 0.7 deaths in this column would be caused by mammography screening of the 53,000 women.

The first data line of the table shows the sponsor's scenario with their estimates of presenting prevalence, T-Scan sensitivity, and mammogram sensitivity. The rest of the table shows other combinations of these parameters.

The most favorable scenario, the sponsor's, would result in a net benefit of 277.2 cancers detected per 0.7 deaths caused. The least favorable scenario at the bottom right would result in 4.3 cancers detected per 0.7 deaths caused.

The most favorable scenario predicts that for the intended use population, to detect one cancer, about 3600 women would get the T-Scan, and 190 would have to be sent for mammography. Under the least favorable scenario from the slide before this, 232,600

women would be T-Scanned, and 12,300 women would be sent for a mammogram.

For our comparison, we chose women who were age 30-39 who have a positive family history, and if the mammogram sensitivity is 70 percent, you would have to mammogram 887 women to detect one cancer. If the sensitivity is actually 45 percent in this group, you would have to mammogram 1379 women, and the sponsor's goal was that T-Scan positive women should have similar probability of cancer as family history positive women.

The prior two slides didn't show what would happen for T-Scan sensitivity equal to zero percent, which would result in 0.7 deaths and no benefit. Depending on T-Scan specificity, 53,000 to 120,000 women per million women would have T-Scan positive and mammogram negative, a possible source of confusion for them.

The FDA method shows that the net benefit of T-Scan is highly dependent on several factors in the intended use population. The first is T-Scan specificity, which might be 88 percent to 95 percent.

The second is the sensitivity of T-Scan, which could be between zero and 26.4 percent.

The presenting prevalence of breast cancer itself depends on three factors. The first is the proportion of women, and their associated relative breast cancer risk, who are clinical breast exam positive, which is poorly known.

The second is the proportion of women, and their associated relative breast cancer risk, who are family history positive, which is well known.

The third is the dependence of clinical breast exam status on family history status, which is unknown.

Finally, the relative benefit of T-Scan depends on mammography sensitivity in the intended use group, which is quite uncertain. Changes in breast cancer screening and diagnosis practices could have an impact on the ultimate usefulness of T-Scan.

So I now return the podium back to Dr. Ron Yustein.

DR. YUSTEIN: You have heard a lot of information in the last hour. I just wanted to kind

of summarize here for you.

Basically, the sponsor provides two studies, two independent studies, to estimate the sensitivity and specificity of their device. They obtained a sensitivity of 26.4 percent. The 25.5 includes the post-menopausal women. Specificity of 94.7 percent. Assuming a prevalence of .15 percent, the relative probability calculation is 4.95, with the lower bound of the 95 percent confidence interval above 2, therefore having met their primary pre-specified endpoint.

Based on these numbers, the sponsor concludes that for every 136 positive T-Scan results, one will be a cancer case, and that this is clinically meaningful compared to the baseline of one in 667 for those in the intended population.

What we will be asking you to focus on this afternoon in your deliberations are some of the issues we have been struggling with.

Number 1: The degree of enrichment in the study, with subjects over the age of 39, those with positive CBE and positive family history, and on the

performance and the results you have seen, especially as it relates to the intended use population.

Number 2: The differences that have been presented to you so far regarding baseline characteristics, differences in sensitivity and specificity results between the U.S. and Israel, and your interpretation of how those may impact the poolability of the data.

Third, the true prevalence rate, what your opinion is on that as it may not affect the relative probability, but it may affect other assessments, including positive predictive value and the number of women with false positive exams.

Next, the risk to health of a false positive result, if any? Then finally, we will be asking you to help us assess the overall risk/benefit ratio of the submission.

With that, FDA concludes their presentation. Thank you.

CHAIRMAN CEDARS: I would like to ask the Panel if they have any questions for the FDA.

DR. MORTIMER: Yes. Could I ask a

question about the risk/benefit slide, slide number 107, and I just -- Maybe I don't totally understand this, but if we look at the number of women to mammograms, that would mean for the CBE negative and the family history negative, there are 12,300 to one. But as I understand it, if we use the calculation of the number -- there are 14 cancers caused for every million women that undergo mammography, then that mean this would be a wash. Am I correct?

DR. BRIGHT: You have to mammogram a million women to get 14 deaths caused by mammography. So when you start looking at the numbers that you have to mammogram to find one cancer, the number of deaths that you cause is really negligible.

Does that answer?

DR. MORTIMER: Yes. Thank you.

CHAIRMAN CEDARS: Any other questions from the Panel?

DR. BERRY: So for Dr. Yustein and Dr. Bright: The 2, the relative probability of 2 -- where did that come from, and why did you come up with that particular number?

We have been arguing about is it 0.0005 or 0.0015. I note that that argument is already 3, the ratio of the two. And if you look at -- Dr. Bright showed a figure from SEER which showed an increase over the age of 30-39 of about fivefold in terms of the relative probability of the prevalence. So if you take a 2 and apply it to a 30-year-old, you increase her -- and it's a positive T-Scan, you increase her risk to the same as an unscreened 33-year-old.

If you take a 35-year-old and apply a factor of 2, you get the risk of an unscreened 39-year-old. So it makes no sense at all to have a constant factor of 2 applied for everyone in the age bracket 30-39. That age bracket itself is a 5.

DR. BRIGHT: I believe the logic for selecting that number has to do with the guidelines put out by the different cancer societies, saying that for women under 40 the physician should discuss with the woman her risk factors and, if she seems to be high risk, family history being a very dominant risk factor, then they should talk about screening with mammogram earlier.

The statistics for women of all ages is that family history positive doubles your risk. For women less than 40, it may even triple your risk. So I think the logic is not about getting them to the risk of 40-year-olds. It is about comparing women who are family history positive versus negative. Does that logic follow for you?

DR. BERRY: I certainly understand that your risk is increased with a family history, for example, but it is much more than 3. If you are a 30-year-old and you have a CA-1 mutation, your risk is 50 times that of a non-mutation. So I certainly understand that. But the question applying a 2 to a 30-year-old is very, very different from applying a 2 to a 39-year-old.

If you accept that 2 is the right thing, then -- If you accept that 2 is the right thing for a 39-year-old, then you ought to insist on something like a 10 for a 30-year-old.

DR. BRIGHT: Well, I think I hear what you are saying about quite a lot of variation across the decade 30-39. But there is also a problem with very

little good solid epidemiologic information about what is the actual rate for each year, what's the effect of the risk factors on each year, because even that big collaborate study, meta-analysis, didn't break it down year by year. They took pretty big chunks of age to come up with their figure. So that's the counter-view.

CHAIRMAN CEDARS: Would the sponsor like to respond to that?

DR. GINOR: If you don't mind, we think it might be better for all of you if we just answer all the questions at once after lunch, as long as that is convenient for everybody.

CHAIRMAN CEDARS: That's fine.

Any other questions from the panel for the FDA? If not, then we will take a break for lunch. I did want to again remind the Panel members not to talk amongst themselves or with outside participants regarding this PMA during the break. We will be back to start at one o'clock.

(Whereupon, the foregoing matter went off the record at 12:13 p.m.)

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

Time: 1:09 p.m.

CHAIRMAN CEDARS: Okay. We would like to go ahead and get the afternoon session started, please. If we can get started, please.

I would like to call the meeting back to order, and I would like to ask the sponsor if they would like to take the podium and answer the questions that were raised before lunch, and let's say that we are going to try to get this covered in 20 minutes, and we will see if we need additional time after that.

DR. GINOR: Welcome back. I believe that probably the most useful thing will be for you to hear from the clinicians and experts as opposed to from me, who I'm sure you are getting kind of sick of hearing from. However, some of the questions that you asked, I think, are questions that I have simple correct and exact answers for, and I think what I would like to do is just give those to you now and let you continue with your debate so that you can have expert opinions on things where you need experts, if that is appropriate for you.

We have a list of a few questions. I want to try to go through them as rapidly as I can, but if you feel I am going through them too rapidly, please let me know.

There was a question that was asked in regard to how many patients refused to participate. I wanted to make sure that I asked the question right. There is no way for us to know exactly if a physician in a clinical site asked a patient, would you be interested in being part of a clinical study and she said no. There is no way for us to have a log of that, and I apologize, but we just don't have a way of knowing that.

There are, I think, two women in the study that started the exam and didn't follow through. There were two women in the study that enrolled and then didn't follow through, but those were time issues, patients that had to go back to work or something like that. That's different than what we were talking about, which is offering a patient to partake before a biopsy and her saying no. Unfortunately, I don't have data on that.

The second question had to do with the type of tumors we were finding in the partition between 30 and 39 and the partition between 40 and 45. There is not a -- They are hard to do great distributions with 87 cancers, but there was not a difference in the type of lesion that was found between the younger and the older. In terms of grade and stage, we don't have those broken down. We are going to keep trying to see if we can get that broken down by the time we speak to you again, if we speak to you again, but we don't that right now in terms of grade and stage.

Cup size in the U.S. and Israel: Was there differences? Yes, there was a difference. The bra cup size in Israel was smaller than in Israel (sic). However, even with the largest bra cup size, the results and the endpoints were still met. They were not met as well, but they were met.

So in regard to whether there is a reason the device should not work in large breasted women, there is no reason to believe that, because currently size D and above was a smaller part of the overall

demographic and, therefore, it is hard for us to make far reaching assumptions on that relationship. But luckily, or appropriately, the device works as it was intended to in that bra cup size as well.

There was a question that was related to that, and a good one, in regard to BMI, body mass index and bra cup size. That was not something that we looked at in this study. That is something that we expect to look at in the multi-year study, because we think that it will play role. There was a question of relationship between bra cup size and overall body mass index, and we think that is an interesting covariate to look at, and will be looked at in the future.

There was a question on different ethnicities and the various types of malignancies that they had in the study. As you saw from the FDA presentation, we had very few cases from African American, Hispanic, American Indian patients. So that certainly, we couldn't break the types of lesions they had.

Racial diversity is one of the things that

initially drove us to be interested in this potential tool in the first place, and we are trying to do several things to work with populations that are ethnically enriched in order to ensure that we get more data.

One of the reasons that we were so supportive of the U.S. Army's interest in the study is that they have a population that is privileged to include 52 percent of their patients ethnically diverse. That's about 45 percent African American and the rest Hispanic, and we are -- One of the reasons that we are still interested in that study is to offer more racial diversity than we would find in the population at large.

We did as part of the PMA -- and I believe that is in your data -- impute the data from the study on the U.S. Census data, so that we could figure out what the result would be if the results from the study were extrapolated to meet the percentages of the various ethnicities in the United States. But of course, that is an imputation, which is not as precise as the multi-year data that we are going to collect in

the longer study.

There was a question about whether the hormonal milieu or the skin or dermatological condition affects EIS. That was something that was looked at with the prior device, the TS-2000, the high sensitivity device, and where the thresholds were on that device you could actually find changes in regard to various changes of that nature.

With the new device, you cannot. Again, the old device operated at a sensitivity of 80-90 percent, and so very small changes could be recognized. Here with the algorithm essentially reversed, those changes are not recognized by the algorithm as large enough to make a difference.

What percentage of T-Scan positive women went on for mammography was asked by one of the clinicians on the Panel. We agreed with FDA up front that it was not appropriate for us to dictate management or follow management, because we did not want physicians to feel that we were already, before having completed the study, telling them that patients need to go off to additional imaging, and we felt that

by mandating that we were doing so before we had proven what we have now proven, and that is that the device does indeed have a strong association with risk.

So we feel much more comfortable saying that now than we did back when we started the study.

There was a question that was asked by Dr. Yustein before, why I said that there was one site that had the technical problems, and in fact it seemed like two, and I should have been a little bit more clear.

It is one site that had two locations. RFW and RJG are the same site. They just had two machines, and they were named differently so that we could keep track of them, but it was one site. The devices were shipped there.

Okay. There was a question about the nine sectors of the breast, and I think that also dovetails quite nicely with a question in regard to some of the more complicated areas of the breast where one would need to look for lesions, for example like in the axilla.

I remind you, the device doesn't have to, is not supposed to, sit upon a lesion and identify it. The device is supposed to measure the behavior of the breast tissue as sampled across the breast and identify areas that are different than expected. Probably the strongest measure is the one that comes from the nipple, which is recorded first, simply because the nipple is the pathway of least resistance across the breast, because everything flows in that direction, the ducts, the nerve tissue and the blood distribution. But we do not pretend that this is a device that you could, you know, put around the breast and look for a lesion. That is the job of the next step in those women that have a risk that requires that kind of analysis.

So in regard to the question with what was done to ensure ethnicity distribution was representative of the population at large, that was not something that we could do in this study, which was designed to show efficacy, and that is what we expect to do in the large study following. It was only imputed.

I believe, unless somebody feels -- Oh, there was a question about ER positivity, and we did not collect that information on the biopsy reports. That is great information to collect in the ongoing studies.

Again, the discussion with FDA in starting this study was the prior device had been approved and shown a relationship between breast cancer detection and safety -- and EIS, and was regarded as safe. When we approached with this new device, safety was no longer a concern, and we had to show efficacy.

We designed this study -- and I should say and correct what may have been said earlier, the FDA did not suggest to us, but rather we suggested with FDA and worked with them on what the primary endpoint should be.

We worked on what would be sufficient to show efficacy in an environment like ours where safety was not a concern, such that we could go out in the clinical world and gather the hundreds of thousands of patients that will be required in order to answer some of these more complex questions. That was what the

study was designed to do. The next study is designed to answer all those more narrow questions which, granted, are of importance.

I believe that that answers all of the questions or at least attempts to answer all of the questions unless someone feels that I neglected their particular question and, if so, I apologize.

CHAIRMAN CEDARS: May I ask the committee if they have additional questions, and some of this may come up for discussion with the FDA discussion questions. But are there any additional questions for the sponsor at this time?

DR. GLASSMAN: One question. I noticed in your data tables that a local institution, George Washington University Hospital, had just two patients. Was that a problem site or why such a small number?

DR. GINOR: It wasn't a problem site. It was just that the device was there quite a bit. If you know the folks there, they are very, very, very busy, and it was hard for us to get them to stop their path to doing biopsies, which they do in a very organized way, and use the device before.

While the exam only takes six minutes to perform in clinical practice, filling out the CRF and getting all the appropriate approvals and so on from the patient takes almost an hour, and it was hard to do at very high flow centers, academic institutions. That was one of the reasons, actually, that it was so much harder to recruit here.

DR. JIANG: There was a question before about why small cancers have higher sensitivity. I didn't hear you address that. I'd like to hear that.

DR. GINOR: That is a good question. Again, I'm answering these in the most basic manner that I can. Then if those become topics that are more interesting, then we can elaborate further.

There are two predominant theories in regard to why smaller lesions do better. One, very large lesions, which tend to do not very well at all on electrical impedance, often have an area of central necrosis, and when you have an area of central necrosis, in fact, the impedance level rises up to the point where you no longer can see the difference. Then you may be looking at the peripheral area where

the angiogenesis that takes place feeds the outside of the tumor, but the center of the tumor essentially is necrosed. So you don't have very good measures on lesions above 3 or 4 centimeters sometimes.

The other issue is that you are trying to concentrate the signal in measuring EIS across an area that rises above a certain threshold, and it appears from measurements done by -- I'll tell you the name in just one second -- that smaller lesions concentrate the flow across a smaller -- the same amount of flow across a smaller area and, therefore, peak across a signal density that is enough to be recognized. Davies -- Dr. Davies is the one that published that article, and I think we might have that information on hand, if you would like to see it.

DR. JIANG: Do we know whether this statement is true for very small cancers, down to what level?

DR. GINOR: The smallest cancers that have been reported with EIS -- and this is a bit tricky, because those cancers, without having some spiculation or some calcifications, would probably not have been

found following EIS -- were 2 to 3 millimeters. But again, those lesions were picked up because they were also on the follow-up spiculated to the point where the mammography or the exam that followed was able to indeed go in there and identify them.

DR. BERRY: The FDA made quite a point in their presentation of the fact that there were only four cancers, and this is across U.S. and Israel -- only four cancers that were detected in the intended population, namely the CBE negative and the family history negative, of which one of those was detected by the device.

Do you agree with those data?

DR. GINOR: I'm not certain what do I agree with those data mean, but --

DR. BERRY: Is it, in fact, the case that there were four cancers in your sensitivity population that were in your intention population? That is, a CBE negative, the family history negative.

DR. GINOR: I'll tell you why I am perplexed by that question. I'm perplexed by that question, because the initial concept behind this

entire study was how to collaboratively develop a method for enriching a study in such a way that would mimic the target population in a way that gave clinicians, statisticians and others a sense that this was a fair representation of the ultimate target population.

The fact that we had any, for example, CBE negative cancers detected in women age 30-39 was happenstance, and we were glad to have it. I wish we had found it, but those data are not -- It's not really fair to pull those patients out, because the whole basis for the study is that they are representative of one another from a clinical point of view, and from a -- You know, as Dr. Stavros said, as Dr. Stojadinovic said, there is no real reason why you would expect that a 41-year-old breast would be different than a 39-year-old breast. So why would you decide that a study all of a sudden becomes invalid, because the patient was 39 as opposed to 41, even though it had been discussed before that that was a representative way to analyze it.

DR. BERRY: I agree with that. I agree

with the 39 and 41, and I don't mind enrichment in that direction. The enrichment in terms of the CBE positives or the family history positives, when that is not the intended use of the device, bothers me.

DR. GINOR: That is a better question. I don't mean better in terms of critiquing your questions. It's a better question for me to deal with from a scientific point of view.

I like that question quite a bit, because as the data shows, we biased the data against ourselves by allowing those palpable lesions. In fact, we generally do better in non-palpable lesions. so there is no reason to believe why including those patients would mean that we have no longer exceeded our relative probability thresholds, as we did.

I agree you that, if the opposite was true and we did terribly in small lesions, missed all small lesions and found only large lesions, one could say, well, you know, you are really just finding the lesions that we are supposed to find on CBE anyway.

The reason we went up to age 45 and the reason we analyzed clinical breast exam positive and

negative patients and lesion size was to show the clinicians, if possible, that this was an additive tool, as was described by Dr. Wapner this morning, a piece in the puzzle to help you where clinical breast exam is weakest, in those areas that are very small and hard to detect by hand.

That has been -- That, in essence, was what drove us to try this model in the first place.

DR. BERRY: So if you go up to 45 in the intended use population but restrict to the CBE negative, family history negative, how many cancers did you have, and what was the --

DR. GINOR: I think this goes back to what you keep saying. Are you asking me if I stand behind the data we presented to FDA? The answer to that is, yes, I do, 100 percent. If there was four cancers reported of which we found one --

DR. BERRY: But that might have been just in the 30-39 and not including the 40-45. Were there extra cancers in the 40-45 that were still in the intended use, even though --

DR. GINOR: Oh, you mean the intended use.

Except for by age would have otherwise been intended use?

DR. BERRY: Yes.

DR. GINOR: That is a good question that deserves for us to look into the data and answer you, and we will do that.

DR. BERRY: All right.

DR. GINOR: Thank you.

DR. MORTIMER: You know, it would be very helpful if this test was able to identify these very, very small lesions, obviously. Amongst the benign biopsies, the 303 benign biopsies that you had, what were the results for those lesions that we know are precursor for breast lesions? I mean, do the adenoses and are they different than the fat necroses that don't cause breast cancer?

DR. GINOR: To me, personally now as a clinician, not as standing behind the pathology, that's a very interesting question, because if the idea is to identify risk, then pre-malignant lesions that put you in a risk category are very, very good things for us to know about.

When we discussed this with FDA, in order to keep the study as clean as possible we did not include things like LCIH, HDA, radial scar, etcetera, as malignant lesions. So we didn't do that analysis. However, that analysis has been done in other papers, and it was actually presented at ACOG this year -- last year, pardon me -- that showed a significant rise in T-Scan positivity from perfectly normal breasts, benign masses, pre-malignant masses, and malignant masses.

So I do believe that that is true, but it's not something that I can say was part of our PMA data. Therefore, I can't state that as a clinical fact in this forum.

CHAIRMAN CEDARS: Do you know if we have that data to review? I didn't see that in your packet, that correlates the positivity with the EIS and progressive increase in extent of lesion.

DR. GINOR: I don't believe you do, because all we have is an abstract that was published by physicians outside of us, which is why I said I don't believe that that is -- Pardon me.

Oh, just to answer your question -- I'm sorry -- not to divert from your question, there were 15 cancers, and kick me or something if I say it wrong. Fifteen cancers which were women 40-45 that were family history negative and five of those were T-Scan positive, 30 percent. Across all ages, excuse me, 15 across all ages that meet the other criteria, and five of those were T-Scan positive. Perhaps that should be looked at.

CHAIRMAN CEDARS: Those were exam negative and history negative or just family history negative?

DR. LENINGTON: They were both CBE negative and family history negative.

CHAIRMAN CEDARS: So 15 total CBE negative, family history negative, and the T-Scan detected five of them?

DR. LENINGTON: That's right.

DR. GINOR: As if it wasn't hard enough answering one question at a time, I'm going to try to answer three at a time.

No, that data was not data that was done by us, monitored by us, analyzed by us and, therefore,

didn't have a place in the PMA, which is why I don't know if it's relevant to discuss it.

CHAIRMAN CEDARS: Any additional questions from the Panel?

There may be -- I appreciate your expeditious use of your time. There may be additional questions that come up during the FDA discussion, and we will certainly give you an opportunity to speak at that time.

If we can shift to the FDA to begin the Panel discussions. The Panel has these questions before them, and if I could just briefly summarize on question one.

This has to do with the estimates that are used by the sponsor to calculate primary effectiveness endpoint, and these estimates include estimates of prevalence, sensitivity and specificity.

So the first question is: Please discuss the clinical significance of the primary effectiveness measure and the result obtained in the overall study population.

Again, this was that equation, and in it

is involved the prevalence in the population, the sensitivity and the specificity as determined by the two arms of the pivotal trial.

DR. BERRY: So this relates to my question for the FDA about how did they come up with the 2. I think the 2 hurdle is much too low -- exactly what it should be is not clear -- and that, of course, the estimate, depending on whether you un-adjust it or adjust it, it was close to 5 versus 2-something.

I think it is much too low and that it absolutely must be associated with age. A 30-year-old is incredibly different from a 39-year-old in terms of risk of breast cancer. So to say a 2 applies, as I said earlier -- a 2 applies for a 39-year-old would mean it should be 10 for a 30-year-old.

DR. SNYDER: I'll take a 180 degree stance on that issue, because what my patients are interested in is when they should start screening and is there any reason to screen earlier than the agreed upon recommendation of age 40.

You know, currently we discuss with them risk factors, and all I can tell them is, if they have

a first degree relative with breast cancer, they have a two times higher incidence of breast cancer; and based on that, the current recommendation is to undergo mammography screening earlier, 10 years before the age of diagnosis of the first degree relative with breast cancer.

So if I am going to avail or allow my patients to avail themselves of entering the screening process early based on family history, then if I have another tool that gives me an equally increased risk factor of 2, I think it is very reasonable for the FDA to have agreed upon that increase risk ratio of being 2, because that is what we are currently using in clinical practice to institute earlier screening. Am I making sense?

CHAIRMAN CEDARS: Let me just clarify. So if I am 32 and my mother or first degree relative had breast cancer at 50, when would you start screening?

DR. SNYDER: Forty.

CHAIRMAN CEDARS: So - But based on this test, you are going to start screening at 32, if she is positive. So it is a different standard, and your

standard is age related, because it's 10 years before the cancer or at age 40. So that is consistent with what is being said here, that it is age specific.

So you would not in that 32-year-old start screening?

DR. SNYDER: Right. You know, when we are talking about odds ratios for a typical hyperplasia or a positive family history, it is not split out by age, 31 versus 35 versus 37. I mean, if we had that data, I think then we could get a reasonable recommendation to give, but it's just broken down as a risk factor. Again, that's the target that they were given to meet.

DR. GLASSMAN: I'd like to look at the 2 from a different standpoint, and that is a little bit as to what happens next. I think the paradigm that we are looking at with the T-Scan is very different than what we do currently in clinical practice.

Someone with a risk of 2 may enter screening earlier, depending on the age of the first degree relative. But if they enter earlier, they tend to enter in general at about age 35. They have one mammogram, and then they come back at age 40, if that

mammogram is clean, and they only have one first degree relative.

The paradigm that seems to be suggested here with the T-Scan device is, if they are positive, they are going to get screened. Next year, based on the reproducibility studies, they are going to be positive again. They are going to be screened again.

So we are in a situation where someone, instead of entering periodic screening at an earlier age, is being committed to annual screening, and I'm a little uncomfortable with that as an outcome based on the prevalence of cancer in the age group.

DR. TAUBE: I agree with that, because the labeling -- The labeling indication is to do this on an annual basis, and I had the same question: Well, what is the expectation of how often? I mean, is this going to consistently be positive, so that even if it is a moment in time and this is an indication of your increased risk at that time, if in fact it is reflecting something that's happening in the breast, then it may become -- it may be positive each time. You are going to have then a mammogram, and on some --

You know, on one of these mammograms, the mammogram is likely to be positive, and then you are going to have a biopsy, which is not risk free.

Based on the data that I am aware of, the biopsy is most likely going to be benign, but you are putting a 30-year-old or even a 35-year-old into this sort of regular non-risk-free environment of going on to a series of tests that can be psychologically disturbing but also physically, and since we don't have data to indicate that it is going to make a difference long term in the outcome and the survival catching it at a very, very early stage versus catching it a little bit later -- It may be worse, but we don't have the data to support that at this point.

DR. SNYDER: I didn't necessarily -- You took the approach of assuming that it is going to necessarily enter them into the screening process that is currently recommended for 40-49-year-olds, which -- I mean, none of us can agree on whether it's every year. It is for me, but it might be every other year for other providers.

I will say that the company is not

advocating that the only approach is to get a mammogram, and they don't know any better than we do sitting here what to do after that first mammogram; because if the mammogram is completely without abnormality, I agree, we don't know what that next step should be. But it doesn't necessarily have to be that they are going to enter now into some sort of routine screening process. We don't know that, right?

CHAIRMAN CEDARS: This raises two questions I have. One is: If we don't know that and the company doesn't know that, what is the expectation for our patients? And we should know that before this gets widespread and used on a yearly basis for patients, because there is that concern.

The second issue gets back to prevalence, which I think is one of the things that has been up for debate between the FDA and the sponsor. Clearly, prevalence impacts on the effectiveness, and it impacts on our interpretation of what to do with that twofold increase, because twofold over what? What's the background risk

So can we have some discussion about those

issues?

DR. MORTIMER: It's my concern about what the standard of care would become, and realizing I'm coming at it from the oncologist's standpoint where we don't do well with false negatives -- would be that these women would be getting MRI scans, and obviously, a lot of negative biopsies as a result that are going to have sequela down the road.

CHAIRMAN CEDARS: Ms. Mayer.

MS. MAYER: Yes. I would like to just comment on the impact on women of false negatives as well, and just introduce the thought that, if you have a patient coming into your office who is healthy according to your breast exam and family history, the anxiety that she feels about breast cancer may be fed by a lot of factors, most of which have nothing to do with the reality of incidence at that age.

I wonder if by encouraging her into an annual test that will sort her into a risk category, either a low risk or a higher risk category, if you are not avoiding -- if it doesn't encourage physicians to avoid their responsibility to realistically explain

to woman who come in highly anxious about risk but with no risk factors what the reality of incidence is, because as far as I know, there are several studies that suggest that women, young women, overestimate their personal risk by a factor of -- I think it's at least 10, if you ask them what do you think your risk in the next five years or 10 years of getting breast cancer.

So I have real concern about how this plays into this and further medicalizes a population of women who are not breast cancer patients and probably never will be, the vast majority. In other words, I think we need to broaden our look at this beyond those cases that are actually found.

I think everybody around the table agrees that that's a benefit for those women, but we have to look at all women here.

CHAIRMAN CEDARS: Dr. Miller.

DR. MILLER: I would second that, and I think, actually, in the discussion about what the appropriate follow-up should be in a -- really, we are talking about a false positive, a screen that's been

done that has identified a patient at risk, but the subsequent evaluation disproves that there is any evidence of cancer.

I would think that it is really going to be more a case of the patient wanting some rigorous follow-up in the time that follows as opposed to what the physician is going to want. I mean, now that she has been elevated to that level, will she really be comforted by the fact that the -- Whatever testing is done beyond the T-Scan, will she be comforted by the fact that it was sufficiently diagnostic that she doesn't, in fact, have some cancer lingering, and that is not an insignificant percentage of women.

DR. BERRY: So embedded in Dr. Bright's voluminous data were risk/benefit issues. If you consider -- Let me take an extreme -- a 30-year-old woman, a 30-year-old woman, 10,000 30-year-old women getting the device, the EIS, 9,998 of them will be not breast cancer cases, but 500 of those will be positive on the T-Scan. The other two will, in fact, be breast cancer cases, and using a sensitivity of 25 percent we will identify on average a half of those.

I am concerned about false negatives, as Musa Mayer is, but I am very, very concerned about the 500 false positives. We heard testimony that the observation of these women was that they weren't affected. If they are anything like women in my life, they would be very much affected. In fact, men in my life would be very much affected.

We hear, okay, so it's only one percent chance, despite the fact that I tested positive; but we hang on that one percent chance and, you know, maybe it's me. I think that -- and if you go to 39-year-old women, change the two to 10, so 10 out of 10,000.

I think this device would do much, much more harm than good.

MS. MAYER: Just to follow up with the other group that we haven't discussed because this is very personal for me, not with this test, of course, but with mammography, my diagnosis with breast cancer was delayed by about 15 months, because my gynecologist interpreted, despite my having a palpable lump, the fact that I had a negative mammogram as

meaning that there was nothing serious going on.

Now I'm still here 17 years after this, fortunately, but I've met over the years a number of women who are no longer alive because of delayed diagnosis. So I am also concerned with those women who are T-Scan negative, but those, I think, roughly 75 percent -- 74 percent of women who do have breast cancers and are T-Scan negative who may be false reassured by this test.

I know the power of that kind of reassurance. You grasp at anything you can find to reassure you that you are okay. So I'm also concerned about an interim group that may be T-Scan positive but mammogram negative, and as I understand the sensitivity of mammography and the claimed sensitivity of this test, there may be tiny little tumors that are too small to show up on mammograms, but that are found on the T-Scan, which means that women won't really have the kind of reassurance.

In other words, that period of anxiety will not have an end to it. In other words, it's the time bomb phenomenon. Maybe I'm walking around with

something, and it's just not big enough yet, or they can't find it or my breasts are too dense. Walking around with this kind of anxiety is a terrible thing for women, and unlike a prenatal test where presumably once the child is born, this can go on for year after year after year.

CHAIRMAN CEDARS: Can we discuss the clinical significance and the impact of covariates in subgroups, as the FDA was talking about? Do you think the covariates should be included in the analyses?

DR. BERRY: I think they should be included. I do accept the sponsor and, I guess, the FDA's position as well that the enrichment is quite acceptable and including Israeli patients, for example -- or women, is acceptable. But it is an appropriate statistical approach to adjust for covariates.

CHAIRMAN CEDARS: And what about the subgroup analyses, the patients in the different -- There's some issues we are going to get into in the next question about the applicability to the intended population. Nancy, did you get all of the answers you needed to this first section?

MS. BROGDON: I believe so. Thank you.

CHAIRMAN CEDARS: The second question has to do with the enrichment, and we have talked about this a great deal, the enrichment of the sensitivity arm and whether or not the final results have applicability to the intended population.

DR. GLASSMAN: I'm a little concerned about that. I agree that the enrichment was appropriate. I wonder, though, based on the data if we almost have replacement rather than enrichment. That is that the enriched group is such a significant percentage that I think it makes it harder to be comfortable that the device will do in 30-39-year-olds what it does in 40-45-year-olds who have a breast lump.

So I'm uncomfortable making that leap of faith. I would have rather had seen maybe a quarter of the patients in the enrichment group rather than, basically, half.

DR. BERRY: Can I add. I'll be you would have been happier to see larger sample sizes in both groups and, if they were 50/50 but, you know, 100

cancers in each group, you would have been much happier.

DR. TAUBE: And they aimed for 100, but they didn't have 100 cases. I mean, the study design said 100 cases.

DR. JIANG: I understand the argument that cancer is very rare in the 30-39 age group and, therefore, a rationale to look at older patients, but does that mean that we don't know what happens to the 30-39 age group or do we know? What I get from this is we don't really know.

CHAIRMAN CEDARS: Let me just make sure I understand your question. We don't know what happens to them in terms of their cancer risk or what happens to them in the face of this study, this piece of equipment?

DR. JIANG: In this equipment, particularly about sensitivity, because we need to assess the sensitivity of this device in 30-39 age group, and we don't have that.

CHAIRMAN CEDARS: Is there a general sense from the Panel that the sensitivity arm with its

enrichment as presented here is, in fact, applicable to the intended use group?

DR. BERRY: Can we put a caveat? I mean, I think the answer, from what I hear people saying, is yes, but there is a reservation about the number of cancers in the intended use group, that the enrichment is okay, but the total number of cancers is not very great, and especially the number in the intended use group is not very great.

CHAIRMAN CEDARS: Yes, see, I would have gotten from the earlier discussion a different answer. I would have thought the consensus would have been that it was not applicable. So I'm a little confused. So maybe if people can expound a little bit.

DR. WEEKS: This is certainly not my area of expertise, but I think the argument has been made that there is no -- There have been offered no plausible physiological reasons why a 42-year-old breast should be different than 37. But when I look at the data, I feel the opposite way, that we need to investigate whether or not there is a reason that they are different as far as this test is concerned and

impedance is concerned, and I'm not reassured by the apparent low sensitivity in the subgroup analysis.

I do accept the reason for doing the enriching, to begin with, but I think it's difficult to ignore the low sensitivity in the subgroup of women who are 30 to 39.

DR. MILLER: I guess I'm confused by what we have in front of us and what we've heard. It looks to me like in our question 2 and the paragraph there that what they are saying is, of the 87 cancers in the sensitivity group, only four of them met the criteria of having no CBE and no family history. But that is not what we heard a few minutes ago from the sponsor, and that would influence me in terms of my conclusions.

CHAIRMAN CEDARS: The sponsor can correct me, but my understanding of the difference between the four and the 15 is the four was in the intended use group between the ages of 30 and 39 with negative family history and negative mass. The 15 was in an expanded age group, 30-45 but no family history and no breast lump. So going to the argument -- It did, yes.

No, the 15 included the four, but it included going up to the older age group with the argument that the breast in a still menstruating woman was not that different in a 43-year-old than a 38-year-old, but at least trying to look at the population with a negative family history and with no palpable lesion.

So that's the difference between the four and the 15. Is that correct? And the four are included in the 15.

DR. ROMERO: In thinking about the question as you have posed it, I think it is a little frustrating to be put in the position to sort of have to give a sense as to how satisfactory these data are when they have been indeed limited by constraints, I think, imposed by the sponsor or by just those who designed the study.

We heard earlier that everybody would have probably preferred a larger sample so that we would have had more statistical power and able to look at subgroup differences with greater rigor. But it was mentioned that that would extend the duration of the study and the cost of the study.

So it is very frustrating. I'm not going to be able to give a very concrete position because that is just not ideal study design, and while we can't have a perfect study design, I design studies myself and you are always making concessions. It really seems that that is an unfortunate one that was made, the fact that the sample size -- or the duration of the study wasn't long enough to permit a sample size that would have indeed enrolled, eventually enrolled, more women in the intended treatment population that ultimately would have produced a greater number of cancer cases.

So I just don't know where to go to. It is very difficult to be in a position of having to come up with a position on imperfect data, and it is really constraints of the study design that I think we are faced with here.

DR. BERRY: So I think you should blame the sponsor. They are supposed to come with compelling data.

DR. ROMERO: Well, I think one other thing is that, if we can't take into account cost

considerations from a patient, consumer, provider perspective, then we shouldn't have to take into account cost considerations from the sponsor's perspective, because they don't want to or don't feel the need to conduct a study for an adequate period of time.

CHAIRMAN CEDARS: May I ask a question, and some of this comes from my ignorance of statistics, and maybe the people who are better at that can help me. But I think this may get to some of our discomfort with this enrichment population and have some tie-in between question 1 and question 2.

One of the things I had about -- was thinking about in terms of the applicability of the enriched population to the intended population gets back to the prevalence issue. My bet would be that the prevalence of cancer in the group that was in the enrichment group in the sensitivity arm is significantly greater than the prevalence in the intended population.

So to me, it's a little bit difficult to apply data generated in a very different population to

the intended population, just based on prevalence alone. Now is that too narrow of a question or does that make sense?

DR. BERRY: I think, based on prevalence alone is fine. But the question is: Is a tumor that is in a 40-45-year-old different than in a 30-39-year-old? The expectation is that that tumor is older in the sense that it took longer to make itself known or to make itself known to the T-Scan, and is that something that means that it is less aggressive and, therefore, different in terms of the sensitivity specificity and different, as somebody said earlier -- I think Sheila said earlier -- in terms of the impact on eventual mortality?

In answer to your question, I don't see that prevalence would have any impact. If a tumor is a tumor, then let's use that and enrich in the population.

DR. TAUBE: But wouldn't prevalence have an impact on the predictive value of a positive test?

DR. BERRY: Oh, that's sure, yes. The FDA made that clear. Yes, it doesn't -- As they said, it

doesn't affect the relative probability calculation, but it does affect greatly the positive predictive value. In fact, roughly speaking, the positive predictive value is proportional to this prevalence.

So if the prevalence is doubled, the positive predictive value is doubled.

CHAIRMAN CEDARS: Yes. I guess that was my concern, that if the prevalence is so different because the enrichment population was so enriched, the population that doesn't meet the intended use is such a large percentage of the total population in the sensitivity arm that the prevalence is so different in that arm that using that arm to interpret data into the intended use population makes me uncomfortable.

DR. BERRY: Yes, but in their calculations they went back -- Even though they based the sensitivity and specificity on the 40-45s, when they did the positive predictive value, etcetera, I think both the sponsor and the FDA, they went back to the characteristics of the 30-39-year-old. So that comes out in the positive predictive value.

CHAIRMAN CEDARS: Did you have a question?

DR. MORTIMER: Yes. I think it would be -- It's unfortunate that the duration of follow-up on this group was 455 days, because it seems to make sense there would be more cancers in the 40-45-year-old group, because if it takes you 10 to 20 years to go from a noninvasive to an invasive cancer, of course, they are going to have a higher likelihood of being found on exam and mammography, and we don't know what the follow-up of all these abnormal T-Scans was.

So I think it's unfortunate that we don't have longer follow-up to know what became of those pre-malignant lesions that may just not have been diagnosable because they were abnormal T-Scans and no follow-up.

DR. GLASSMAN: Getting back to the prevalence issue, one thing that we haven't really talked about is the way I see prevalence in this study is that after the first round of T-Scans, we really don't have prevalence anymore. We have a modified incidence. That is, the T-Scan device has found the cancers it is going to find, and missed the cancers it is going to miss.

Now the ones it missed will grow, and it may be that they will pick them up in another year. But the new cancers that appear are incident cancers, which tend to be at a rate that is much lower than the prevalence rate. So we really need to talk not only about prevalence but after the first year about modified incidence, which is much lower, which makes the positive predictive value of a positive test lower after the first year.

DR. BERRY: They are talking about only the first test. So a woman who is between 30 and 39 gets her first T-Scan. That's what they are talking about. I completely agree that, if she comes back again and she had a negative the first time, that probably her prevalence is a little bit less, as you say.

DR. TAUBE: But the labeling indicates that it should be an annual test, and I think we can't forget that, especially when we get to that part of the discussion.

MS. GEORGE: Two quick questions. One: There was a comment about the data. In the protocol

it actually identified 1500 exams, and in the data I saw 1900 exams. So it sounds like they actually did more exams than what was identified.

The second thing was, in the labeling, I believe it doesn't say annual. I thought it said that it was to be done when you do the CBE. So if the doctor decides to do it every three years, then it would be every three years.

CHAIRMAN CEDARS: Although I think recommendations -- If we had the list of the recommendations up there, from 30-39 is for annual CBE. So --

MS. BROGDON: I realize this is not a portion of the agenda where the firm should be weighing in, but the firm appears to be disagreeing about the number of exams done, and whether they were repeats.

DR. GINOR: And here's the firm. I would love to say that all the points that you are making don't make any sense. I think they do make sense. I'm just not sure they make sense entirely in the context of what we are discussing.

I feel a responsibility to express some of these things, but I need to make sure that I'm not overstepping my bounds. So throw stuff or tell me.

MS. BROGDON: I think you need to focus on the specific thing you had a disagreement with.

DR. GINOR: Right. So for example, there is no reason to expect, and we actually have said time and time again, that a woman who is T-Scan positive -- that is, a woman who goes to her gynecologist; she has something physiologically going on with her breast, has a mammogram or an ultrasound or an MRI or whatever it is that the radiologists ultimately decided to do, and it is normal, would then have that follow-up again and again and again.

That is not what we are supposed to be discussing, but secondly, that is not the indication. Now if her T-Scan is red again next year, there is something going on, and if she has a mammogram or a T-Scan or an ultrasound or a MRI again, that's probably a valuable thing.

I would suggest also two other things that re related exactly to this data. One, for prevalence

to significantly turn into incidence, you have to expect (a) a sensitivity of 100 percent and (b) an attrition of the product to 100 percent of all women in the United States within a relatively short period of time; and you have to remember that what is different here as opposed to other situations where prevalence is ultimately replaced by incidence is that we have new women graduating into -- from the zero to 30 into the 31 age group where they would get the first T-Scan.

Most studies show -- I think all studies show that your first screening exam either at 40 or at 30 shows much more of a disease prevalence than ongoing, because you are still benefitting from that sort of 30 years of incidence. I think we should keep that in mind, because that would change, I think, the numbers you are doing.

Keep in mind how many baseline mammograms you do at age 35 and, if you calculate the prevalence on that, you will find the prevalence here is a lot higher. I just want to make sure that those numbers stay in focus, because I thought that was kind of

drifting away.

CHAIRMAN CEDARS: Thank you.

DR. JIANG: Can I ask a question related to that?

CHAIRMAN CEDARS: Sure.

DR. JIANG: So I'm kind of confused. i wonder if you could help me understand. So this is comparing to family history positive. If a woman is family history positive, she is always positive. So she just entered a screening cycle earlier.

Now with T-Scan, if she becomes positive, that's five percent of the population that enters into it. So there are two possibilities the second year around. One is that the same five percent of women still being positive. So that is a situation similar to the family history scenario.

The second possibility is an overlapping different set of five percent of the patients becomes positive. If that is the case, are there going to be more than five percent of the people enter the screening scenario earlier? So in another word, the people who are positive the first year around, the

second year they were not positive -- would they be screened again? So they would be screened only once?

DR. GINOR: Exactly. That's the point that I was trying to make, is we are actually physically measuring something. As opposed to like BRCA which is a risk you carry for life or a genetic risk you carry for life, family history, we are measuring something specific, and we are hoping that that is either something that goes away or, if it remains, we assume that there is something going on that needs to be looked at.

So you are correct. It's a one-time screening.

DR, TAUBE: But on page 151 of the Panel pack, it specifically says women who have positive T-Scan ED results but whose subsequent mammograms or ultrasound examination do not detect any lesions are considered to be at average risk for breast cancer. These women, like other average risk women their age, should continue to have T-Scan ED examinations after each CBE.

DR. GINOR: I'm glad you pointed that out.

Maybe I answered the question wrong. Were you asking if they would have a mammogram every year or whether they would have a T-Scan every year?

DR. JIANG: I was asking about mammograms.

DR. GINOR: I thought so.

DR. JIANG: Because a woman may be positive with T-Scan one year -- You know, the woman would have increased anxiety. Maybe she wants to be continuously screened with mammograms.

DR. GINOR: Correct. She might want to, but I don't think that clinically that would necessarily be the right decision. this is not a lifetime risk marker. It is not a genetic marker. We are actually, as I say, measuring something, and that's something that has been proven relatively strongly.

Again, I think the issue here is comparing it to other methods by which we recommend screening, family history, year after year starting at whatever age it is, if it's two family relatives, for example, or any baseline at 35. All of those have a much, much, much lower yield than we do, and I think that's

where things are getting a little bit cloudy, and I just want to make sure that that is kept in mind, is that we must kind of compare apples to apples here.

MS. MAYER: Just as a follow-up question on that: So a woman has a positive T-Scan, a negative mammogram. Is it possible or not possible that the T-Scan may be picking up on something that the mammogram is not?

DR. GINOR: It is possible, and what I would suggest -- and perhaps, since it is not my job to be involved in the discussion, as much as I would love to, I think that a good analogy might be for some of the gynecologists on the panel to discuss, for example, the similarity of this to Pap.

You know, the numbers that we are discussing are not very dissimilar than what we routinely do. Dr. Wapner talked about it in regard to Down syndrome, but you know, the same is true for Pap, is you might have atypia. You might follow on and have colposcopy. That colposcopy might not find something. You have atypia again. You go for colposcopy again. But the level of risk warrants that

measured level of things --

MS. MAYER: I don't dispute that, but what I am trying to get at is what I was saying before. Is it possible for T-Scan to pick up a smaller lesion than a mammogram can find?

DR. GINOR: Yes. In fact, I hope it does, because I hope that patient will next year come in and have a mammogram, and then it will be found as opposed to five or six years later.

MS. MAYER: So given that, doesn't it make sense to continue with mammograms, if you have a positive scan and a negative mammogram?

DR. GINOR: I would love to say that, but despite some of the things that were said in regard to the sponsor taking blame, I don't feel that I can say that in a way that is clinically significant until I show you five-year data.

MS. MAYER: Right.

DR. GINOR: And that is something that, you know -- This is a four-year, 30-center, multi-thousand patient study. No one was cutting corners. In fact, this is probably one of the largest studies

that was conducted with respect to the risk of breast cancer in younger women.

There is a reason why we still rely on CBE. Doing studies of the magnitude we all want are virtually impossible, and to be perfectly honest, it has nothing to do with money. It has to do with time and management.

CHAIRMAN CEDARS: Thank you. Dr. Miller.

DR. MILLER: I was just going to say that -- You know, I was going to make the same point, that relative to other screening tests, including prenatal diagnosis, serial screening exams do have some value, that there is -- I wouldn't anticipate that this would just be a one-time thing. I would anticipate that it would be serial. Whether it is annually or, you know, every couple of years, there is going to be a desire to follow up on this.

DR. WEEKS: I would say that I would agree 00 percent. I will say I'm not sure I like the analogy with Down syndrome screening, because once a patient is screened positive, they go on to a test often that is diagnostic, and that's the end of it.

It is not an annual phenomenon. The ones that choose not to have the diagnostic test actually end up getting many ultrasounds and other tests because of residual anxiety.

So -- and I'm a little confused. The T-Scan -- Once they are T-Scan positive, based on everything we have heard, they are T-Scan positive with their first test, their mammogram is negative, there is every expectation that their next T-Scan will be positive is how we understand it, which then necessarily means the patient will have other testing done.

For the patient that is anxious once they are T-Scan positive, if the idea is that it is most efficient for small lesions, then I wonder if the patient will actually be satisfied with annual follow-up. Is it going to be six months? It sort of opens up a whole bunch of questions that I don't think we can answer, but it's a significant problem.

CHAIRMAN CEDARS: Dr. Snyder.

DR. SNYDER: Yes. I mean, I agree with Dr. Weeks. I mean, nothing with the data that we have

shown tells us what to do with the result. I mean, basically, you know, if ongoing follow-up, what do you do the next year? I mean, that data doesn't exist.

I keep going back to the statement made earlier, more harm than good. I would actually like to ask Dr. Berry this question, because as I was looking at the data -- I mean, even when we do a mammogram in a 50-year-old, when we do a mammogram in a 40-year-old, we've got a significant false negative rate. But as I looked at their data, the ratio of cancers found per study ordered was still a little bit better than the cancers to mammograms found in the population we are currently recommending mammographic screening to, and that's the 40-49-year-old age group.

Am I interpreting the data that they did, comparing the number -- you know, given a positive T-Scan, the chances of having a cancer, it was still a little bit better, at least equal to, the chances of finding a cancer with the mammogram.

DR. BERRY: In comparison to mammograms, the T-Scan has greater specificity, but much lower sensitivity. So if there is a cancer there, it is

less likely to find it. It will be more false negatives.

CHAIRMAN CEDARS: Before we go on to the next question, let me just see if I can summarize --

DR. BERRY: Excuse me, Dr. Cedars. Can I just address one thing about this repeated -- In terms of the "harm than good," if we are doing repeats, and Dr. Jiang is correct -- or he gave two possibilities, one possibility that we are finding the positives among the non-cancers will be distinct from one time to the next.

The first time we do these 10,000 women, we are going to find 500 approximately that are false positives. The next time, if they are distinct, we are going to find another 500, then another 500. Imagine doing this 10 times.

We are going to find half of the population who have some level of anxiety, maybe not a great deal of anxiety, but we are taking this -- You know, I'd love to be in the thirties again. We are taking this wonderful decade and making it somewhat less wonderful.

CHAIRMAN CEDARS: Okay. I think that there is some level of discomfort with the applicability of the enrichment population, but I get the general sense that the Panel is willing to accept that population in its results.

Then again from the first question, that the covariates should be included, but that there was not a sense that we couldn't put the intended groups together to represent the study population.

Nancy, were there other questions before we go on to 3?

MS. BROGDON: No, that is fine. Thank you.

CHAIRMAN CEDARS: The third question had to do with the different sites in the United States and Israel, and you have a copy of the table in your packet looking at the sensitivity in the U.S. and the sensitivity in Israel, both including and excluding the post-menopausal women, which were relatively few. So it didn't change it significantly.

So the question was: Did you feel that the difference in patient characteristics was

represented and whether or not these -- you can actually combine the two groups or did you have discomfort about the differences between the U.S. and the Israeli populations?

DR. HILLARD: I may not be understanding the statistics completely, and that is certainly possible. But when I combine the information that tells me that there were differences in the women in the U.S. compared with the women in Israel, compared to breast size, cup size, and in particular with the issue of sensitivity in the 30-39-year-old group, and find that there were, if I am remembering correctly, zero cancers found in that group in the intended population, which is the 30-39-year-old women with negative exam and negative family history in the U.S. -- So that's the intended population.

So I am -- When I combine 2 and 3 questions, I am more uncomfortable.

CHAIRMAN CEDARS: And there were some questions raised about ethnicity. So while there was a difference in cup size, even though we don't have the data, I would argue there is probably also a

difference in BMI between the two countries, given the rise in obesity in the U.S., and that gets to some of the ethnicity issues that were raised.

So again, for the U.S. population does that raise concerns for people among the Panel?

DR. ROMERO: Yes. I mean, I think we didn't have much time to look at the data presented by FDA scientists, since -- due to limited time, I believe. but in looking over the analyses that they presented when they broke out the study by the two countries, it is really disturbing.

I mean, if we don't -- and I do understand that sites are pooled, but at the same time comparisons are made regularly between sites in multi-center studies, and when you have not just sites within a country but you have sites in different countries, there are other factors to be taken into account that I assume in looking through the data there weren't -- those data weren't collected.

The one area where that was made clear was just in ethnicity as self-reported by individuals in Israel. So when I look at the data that the FDA have

presented in comparing these groups where we have risk ratios or, as described here, relative probabilities with confidence intervals that are below 1, it is really concerning to me that that is not something that the company would be concerned about as well.

DR. BERRY: So this is probably among the most difficult of all scientific statistical issues. Can you look at subsets? A standard approach which the company has followed is that, by the protocol, this is a multi-center trial. They are combining the results from the various centers, and they are putting them together to have an overall estimate.

I, for one, accept that. It is not necessarily the right answer. There may be differences in Israel that have to do with cup size and ethnicity, etcetera, but -- and if you look at this, it's kind of interesting. The sponsor gets P=.06, and the FDA gets P=.04.

If you believe -- If you are naive enough to believe that .05 is dictated by God, you know, you get these two -- I mean, it's not. It's completely arbitrary.

I take it that the per protocol analysis of combining is the appropriate one. What does, however, bother me is the intended use and the CBE and the family history.

CHAIRMAN CEDARS: Any other comments about the U.S.-Israeli data? So again, I think a general sense that, again, some dis-ease but that the intention to treat and combining the data, because the protocols were the same across the data is acceptable. Is that correct?

MS. BROGDON: Would it be possible to poll the Panel, because we would like to hear a little bit more discussion on this really important question?

CHAIRMAN CEDARS: Okay. Can we do that, starting with Dr. Mortimer.

DR. MORTIMER: I'm comfortable with combining the population.

CHAIRMAN CEDARS: I'm sorry. Dr. Goldberg.

DR. GOLDBERG: I would be, too. I think if you are pooling the data from the two different countries and you are coming up with an average

number, I would agree with that.

DR. WEEKS: I am not a statistician. So I can't speak to that. I think that the methodology is fine, but I have a great deal of concern about the -- when you look at the subgroup analysis, I think you can -- It's perfectly fine for discovering new hypotheses. It really looks like we have to ask the question: Is the U.S. population-Israeli population different?

When I look at this data, I am not at all convinced that combining it and using the performance, generalizing the performance to the U.S. population will actually hold true in the future.

So, yes, I think, as the study was set out, the a priori assumptions -- I accept that, but this causes me a great deal of concern.

DR. BERRY: I agree with Dr. Weeks.

CHAIRMAN CEDARS: Dr. Glassman.

DR. GLASSMAN: I also agree with Dr. Weeks. I think that it is appropriate to pool the data. I think, however, that the two subpopulations are probably different with all of those very thin

people in Israel, and it may be that with this technology that that difference may be significant, but we can't prove it.

DR. JIANG: I will follow that. I think it is appropriate to pool the data, but what this says to me is that we really don't have a very good handle on the exact sensitivity. There is a lot -- great uncertainty in estimating that.

DR. MILLER: I am going to go along with what the other panel members have said. I find myself not as concerned about the fact that of the four cancers that were detected, none of them were in the U.S. and none of them were in the age appropriate group.

I find myself more concerned about the fact that there are -- What the Israeli population tells us is there are some distinct characteristics about that population that are different than the U.S. population, and in a fairly dramatic way.

I am a little bit disappointed that more attention wasn't paid to ferreting out what those characteristics are so that we can better understand

whether or not that might mean that the use of this technology in this country should be different, specifically getting back to the issue of BMI and larger breasted women and how that applies to the sensitivity and specificity of this technology.

DR. SNYDER: I agree. I think, you know, my naivete makes me compelled to believe the pooled data much better than any of the analyses at these very small numbers.

DR. TAUBE: I agree with what Don Berry said before about the intent to treat or the intent to analyze in this case, that you have to look at all of the patients you took in. But I think the interpretation and the application to the population has to take into consideration the differences.

DR. HILLARD: I agree with Dr. Weeks' statements.

CHAIRMAN CEDARS: Okay, and I -- Oh, I'm sorry.

MS. MAYER: I, too, agree with the statistical point that is being made about analysis, but I have to say that I have continuing concern about

recommendations for blanket use of anything in medicine. I think we over-test, and we over-treat, and I think what this data suggests -- doesn't prove anything -- is that there are subgroups that may be at much higher risk, and we don't know that yet.

We don't know from that data. But there is enough here to make me say I want more data. I want more study. Hopefully, the study that is currently underway will provide some of that.

CHAIRMAN CEDARS: Dr. Romero.

DR. ROMERO: I think the pooling the data and the interpretation of the findings from subgroup analyses are two different things. I think multi-center -- multi-site studies are done always with the intention to pool the data, but with a caveat that differences will be explored between sites.

So, of course, it is acceptable to conduct a study where the plan is to pool the data, but once the analysis is conducted and there are site differences, and we have a site effect here, I think a decision has to be made as to whether -- you know, how to best move forward.

So one can say that it is appropriate to pool the data and at the same time feel that findings from having analyzed those pooled data are of concern, and that's where I stand.

CHAIRMAN CEDARS: And I am sorry, Ms. George.

MS. GEORGE: Well, I think the sponsor really went through in their protocol and defined that they were going to have the combined, that they were going to have 1000 from the U.S. and then the 500 from elsewhere. So I think it was clear back in March of 2003 when they defined the protocol exactly what they were going to do, and that's what they followed through with. So I think it is appropriate.

DR. BERRY: So I just want to comment on something that Dr. Miller said. I'm not sure I got it, but he said there were four cancers, none in the U.S. Just my impression of what the data show, the four cancers that we are talking about in the 30-39-year group, there were two of those in the U.S., and there were two in Israel.

One of the two in Israel was detected by

the T-Scan. Neither of the two in the U.S. was detected. That's the one in four. There is an additional 11 in the 40-45 group, of which four of those -- and we don't know whether they are U.S. or Israel -- and four of those were detected. So hence, the five out of 15.

CHAIRMAN CEDARS: Did you get the information that you wanted?

MS. BROGDON: Yes. Thank you.

CHAIRMAN CEDARS: Okay. If we can go to the next question, which had to do with the technical difficulties, and there were several questions about this this morning, but the question was specifically raised, because there were 37 cancers that were excluded from the sensitivity arm, which was 51 percent of the cancers were excluded because of technical difficulties, if I am reading that correctly.

So the question was -- or 19 cancer cases were excluded from the U.S. site and 0.7 excluded from -- versus the specificity arm. So the question was, I guess, whether or not that was a concern.

We heard earlier this morning that that was due to one site that had two locations, each of which had a machine that was not properly functioning, and there wasn't recognition that it wasn't properly functioning because of the absence of visual response.

So are there any additional questions related to that?

DR. TAUBE: The malfunctioning machines, I think, were only in the sensitivity arm and not in the --

CHAIRMAN CEDARS: Correct, and that's where the high rate of exclusion for technical issues was, in the sensitivity arm. Dr. Glassman?

DR. GLASSMAN: I don't see that as introducing a bias so much as an unfortunate decrease in the sample size that may have been -- I don't know that critical is the word, but it certainly would have given more power to the statistics.

CHAIRMAN CEDARS: Nancy, do you have any other questions on that?

MS. BROGDON: What is the Panel's consensus on the question of whether this created

bias?

CHAIRMAN CEDARS: Can we poll the Panel on that? Ms. George, do you believe removing those 19 cancers due to technical issues is an issue?

MS. GEORGE: I don't think so, because I think they did all their calculations based off of removing those, and that, at was stated by Dr. Glassman, was unfortunate and that, you know, maybe in future with tests for all of our sponsors is to look at ways to be able to catch that sooner, but --

CHAIRMAN CEDARS: Dr. Goldberg?

DR. GOLDBERG: I don't believe that created any undue bias.

DR. MORTIMER: I agree.

DR. WEEKS: Because I think there is a trend toward decreased sensitivity in the U.S. population, and just about all of them on the U.S. side, I think it does potentially introduce some bias, but I don't feel qualified to say whether or not it would be statistically significant.

DR. BERRY: I'm okay with excluding.

CHAIRMAN CEDARS: Dr. Glassman?

DR. GLASSMAN: I don't see a problem there.

DR. JIANG: Nor do I.

DR. MILLER: No problem.

DR. SNYDER: No problem.

DR. TAUBE: Not a problem.

DR. HILLARD: No problem.

MS. MAYER: No problem.

DR. ROMERO: Same.

CHAIRMAN CEDARS: Okay. Question 5 has to do with adverse events, and it had to do with T-Scan positive patients, additional mammograms that would be conducted.

We did discuss this a bit earlier with the first question, I believe, but would there be any additional risks of the additional mammograms in the women age 30-39, taking into account for any woman, and assuming again, as we read, that T-Scan is intended for use on a yearly basis?

I think the concern here is just that, if someone is once T-Scan positive, always T-Scan positive, then the sort of scenario of then following

up with more additional and potentially invasive, more diagnostic tests becomes an issue.

So, Dr. Glassman, and then --

DR. GLASSMAN: As a breast imager, I finally have a question I'm actually qualified to talk about.

I think there is -- In terms of life risk from mammography, it is negligible. I think doses are lower. I think, if you go back to the Atomic Bomb Casualty Commission reports from Hiroshima and Nagasaki, all of the excess breast cancer that occurred, occurred in women who received a single dose of radiation under age 25. So it is a different population than we are talking about here.

The real risk of the mammograms and the ultrasounds and ultimately probably a number of breast MR exams with contrast is the risk of benign biopsy, and I don't know that we've got a handle on what that risk will be.

I can tell you that, when we look at breast MRIs, which I look at on a daily basis, we don't have really good criteria for what constitutes a

biopsy. But one of the things that plays into the decision is pre-test probability. That is, why are you here for the test?

If you have a known cancer and this is a staging exam, almost everything gets biopsied. If you are a screening because you are a lady from the suburbs with more money than sense and insists on the test, almost nothing gets biopsied for the same appearance.

Here, we've got a situation where we believe, if this goes forward, that this is a high risk patient. So I think there will be a not insignificant number of biopsies, most of which will be benign.

CHAIRMAN CEDARS: I'm sorry. Ms. Mayer.

MS. MAYER: So just to follow on that to talk about the impact of the sort of chain of screening, as I see it, it is really like one -- a positive T-Scan leading to a mammogram that, let's say, may be equivocal but may be accompanied by a sonogram that may ultimately end up with MRI that may or may not ultimately end up in biopsy.

That's a very traumatic sequence for any woman to go through, and I'm really concerned about subjecting large numbers of healthy women to sort of entering that chain; because I know how hard it is to walk away from that or to say no to that, once you are engaged. I've been there.

It concerns me, as it concerns me with all early screening tests, is that we run the risk of traumatizing a large number of healthy women, and for the possible benefit of detecting a few cancers. That's where the issue of prevalence is really significant here, because, obviously, when considering the risk versus benefit, a disease which has a significant prevalence -- you can make a good argument for that.

The issue of whose version of prevalence we are going to accept, since they are so very different, is to me still up in the air. I'd like to hear more -- I'd like to hear what the sense of the Panel is about that. I realize that is not a question that is being addressed here, but anyway I'm rambling.

CHAIRMAN CEDARS: Well, it is to some

extent, because prevalence goes into their calculation in the performance of the algorithms.

DR. SNYDER: I'm going to re-ask my question that I asked earlier. Dr. Berry and everyone with a lot of statistical expertise, if you go to Panel pack page 81 and -- I just can't refer to which slide. We saw this earlier today in the presentations, but it is a table dealing with relative risk and absolute risk.

Again, if we take that the T-Scan positive patients, if they had that relative risk of 4.95, their absolute risk for breast cancer was one in 136. If that relative risk, even in worse case scenario, had gone down to 2, then it would still have been in the range of an absolute risk of about one in 400, which is what we currently are making our 40-49-year-olds go through.

Now again, I'm in the trenches, and I'm discussing with patients, and I agree, the amount of angst that all of this causes. But again, if I can tell somebody that their relative risk is significantly increased over the background, it

doesn't necessarily mean I need to start doing other imaging procedures, because we don't know the answer to that question. You know, what is it that we as clinicians are supposed to be doing in response to this test?

From that standpoint, I agree that this is premature, but I think my patients would like to know if their relative risk is significantly increased beyond their background risk. Am I interpreting this data correct? The 4.95 relative risk, even if you take it down to 2.0 relative risk, they are still in that same range of the patients that we are routinely asking to undergo imaging.

DR. BERRY: So I think you are interpreting it correctly. Back to Musa Mayer -- it is related to Musa Mayer's comment, and the question of the .0015 versus the .0005.

I did an independent thing, quite separate from this Panel, in a paper that I wrote published in JNCI looking at the SEER data. This was in relation to building a model to do an assessment of genetic risk, probability of carrying mutations, especially

important for breast cancers that are detected in the thirties and at young ages.

In my assessment of the SEER data, I agree almost completely with the FDA that the average over this period, the period of the thirties, per year is the .0005. If you look at a woman who is 30, it is .0002. A woman who is 39 is .0010.

So to your point, when you get to the one in 333, which was above the cut for you, that is based on the .0015, which I don't get for any of the women in this age group. In fact, I have to get up to about like age 46 before I see something like that.

So doubling that gets to the .003 for the prevalence. But you are right that -- The .003 comes from doubling the .0015. If you double the .0005, you get to .001, which is one in 1000, which doesn't get to your criterion.

On the other hand, if it were a 5, a ratio of 5, the unadjusted, then you would have to get up -- You know, you would cross the boundary for women that are older than 35 or so, but not for women younger than 35.

CHAIRMAN CEDARS: I mean, I also think Dr. Snyder gets back to the issue of the absolute risk, and that is why the prevalence is so important. The other thing which you mentioned there is the adjusted risk, because if all the other covariates are things you can get by history, then the test is only of value above and beyond what you can get by history.

So I think it was the FDA who prepared the table where they looked at each thing added independently and, if you took all of the covariates and then added the T-Scan, you are right at 2, which then gets -- with a confidence interval that was under 1, as I recall.

So that then becomes very relevant (a) as it is a statistically significant increase, if the confidence interval included 1; and (b) if the prevalence is, in fact, lower, is the absolute risk rise to a level that concerns you enough.

DR. GINOR: A number of the clinicians have wondered if it would be appropriate for them to weigh in on some of these questions, and I believe

that was something that was discussed. I don't know what the procedure for that is.

CHAIRMAN CEDARS: Not at this time.

Were there any other comments that the Panel had?

DR. GOLDBERG: I don't know that it is creating any undue potential risks. I mean, if the risk is a biopsy, I don't know that it creates anymore biopsy than other screening modalities. I mean, if we have an abnormal mammogram and we go to ultrasound or MR next that's negative, you are really not going to go to biopsy. You will go to short term follow-up. If it's a bi-rad 3 classification, you go to short interval follow-up so you assure stability.

If you have a positive T-Scan and you go to the next modality, whether it is mammography or MR, and it is still negative, you are still at the same level of care as with the abnormal mammogram. So I'm not sure that this device is really going to create any undue or any increased potential risk.

CHAIRMAN CEDARS: Dr. Mortimer.

DR. MORTIMER: I just am going to go to

what Musa Mayer said earlier. These women are so angst ridden by knowing they have an abnormality, and yes, you know, if you look at the data objectively, you have a negative MR. You have a negative mammogram. So what else could you do. But you can just, of course, see the ductoscopies, the four quadrant fine needle aspirations, the ductal lavage.

These are accepted techniques and, if you figure one in three women in this country think they are going to die of breast cancer, erroneously, I can't imagine that people would sit on an abnormal --

DR. TAUBE: Yes, and I think the issue of whether you are going to be doing more procedures is -- - You are going to be doing more procedures, because this population is not normally being screened. So now you are saying you are bringing in all the women age 30-39 and so you are going to be doing lots and lots of procedures on these women for an intangible benefit, if any. I shouldn't say intangible -- for an unknowable benefit.

CHAIRMAN CEDARS: Dr. Snyder.

DR. SNYDER: Well, that's the problem. I

mean, what we really want is to see something that is going to give us a decreased mortality odds ratio. You know, we're close to having that information.

So I don't know. I mean, we can't even guess whether there's going to be a tangible benefit or not.

CHAIRMAN CEDARS: Ms. George.

MS. GEORGE: A question for those of you that are the doctors in this. One of the things I was thinking of is that the product seems to have a formality about asking a lot of the questions that, at least when I've gone in to see my OB/GYN, I don't remember the formality of being asked about the family history to the extent that the T-Scan seems to, and the formality of capturing the Gail Model, which I am not real knowledgeable on, and all that. I'm wondering if that is an aid in the process.

The second thing I was thinking about is: Again, I know everybody keeps saying annual, but it does say in the data that at 20-39 you only go for your CBE every three years. So you are assuming -- and if we are talking the 30-39, I believe I heard it

stated that the baseline is at 35. So you are really only talking a five-year time frame of potentially adding additional screens, if I understand everything that you guys are all explaining.

Sorry, I'm more on the technical side than I am on the clinical side.

CHAIRMAN CEDARS: Russ, do you want to answer that?

DR. SNYDER: Well, yes. I mean, pretty much everyone -- There is no such thing as a baseline at 35. I mean, we start recommending annual -- or we start recommending that they begin screening at age 40.

CHAIRMAN CEDARS: Make sure -- because you are talking at cross purposes in terms of mammograms and exam, clinical breast exam.

DR. SNYDER: Oh, right. I think pretty much standard care is a clinical breast exam every time the patient comes in and, if that's yearly, it's yearly.

The other comment was -- I mean, I don't think we should think of this as a benefit for doing

what we should be doing already.

CHAIRMAN CEDARS: Ms. Mayer.

MS. MAYER: In the years I have worked as an advocate, I have seen a real change in the awareness in the medical community of breast cancer in young women in this age group. That's happened in part because of advocacy, and there has been some interesting research in breast cancer in young women. It is really gratifying to see, and it is gratifying to see also that the mortality has gone down actually more in the younger age groups than it has in older women, and the incidence has remained stable and not -- - as far as the SEER data goes, and not as -- Parenthetically, the Mirabel website claims that it is increasing, but that is not my understanding at all.

CHAIRMAN CEDARS: Any other comments from the Panel before I ask the sponsor for their response? Okay. Did you have a response to this discussion?

DR. GINOR: I think Vivian Dickerson wanted to make a comment, and I think she will be followed by Dr. Stojadinovic.

CHAIRMAN CEDARS: And if I could please

ask you to keep your comments brief.

DR. DICKERSON: You may, and I will comply.

I have a couple of things I would like to say. First of all, I am not a statistician. However, I am just appalled by the continued confounding of incidence and prevalence. Those are not the same things. Those are the entire reason why you see different data from the FDA and different data from Mirabel. We are using prevalence data. The SEER data are incidence data.

Having said that, let me say something else. That is, I have to echo what Dr. Snyder said earlier. What we are recommending, if we do not accept this technology such as it is, recognizing there are many, many excellent comments that have been made and suggestions in terms of improvement, which I am sure will happen as time goes on, we are going back to what we have now, which is nothing.

I would suggest that, if young women do not go home from their clinical breast exam with anxiety, they simply do not understand what is going

on, because that exam can offer them nothing in terms of reassurance. And if they feel -- If they know that there are risks of having a breast cancer in this age group, the mere fact that this is a technology, that it is an instrument, that it is a piece of something that is not my hands, yes, that may raise their anxiety, but it doesn't change the picture one iota.

There is anxiety in this population, and I simply have nothing to offer them. So I really personally do not wish to wait five years for more data. I wish to have this device now.

DR. STOJADINOVIC: My comments, too, will be brief. I appreciate the opportunity to make a second round at this. Thank you. Thank you again for the opportunity to state a brief aspect of my thoughts.

We are challenged by, especially my organization, a predominantly young, ethically diverse population, and we struggle with the challenge of identifying women who we can screen and manage in an optimal way.

Our default clinical standard that has

been alluded to is clinical breast exam. So if I'm hearing you correctly, we are satisfied with a current standard where we have 70 percent of cancer self-detected in a group of population, and we are willing to trade that for anxiety, or not willing to trade that for anxiety. I submit that perhaps we should give that some reflection.

The other thing is looking at this in a rigorous way, this was a group of experts that got together with a direction from the agency and agreement among those that discussed it to come up with a primary endpoint and to develop a model and a design with which to either achieve it or fail to achieve it.

So the question is not about follow-up data or follow-up years, because this is a single point in time study. That is the way it was designed to assess if the device is safe and effective to identify risk at one point in time.

We are now conducting the multi-year study to assess what the interval cancer rate and what we do over time, but if I could just have you put your heads