DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
OFFICE OF DEVICE EVALUATION
CENTER FOR DEVICES AND RADIOLOGIC HEALTH

RADIOLOGICAL DEVICES PANEL MEETING

Monday, November 17, 1997

Proceedings By:

CASET Associates, Ltd.
10201 Lee Highway, Suite 160
Fairfax, VA 22030
(703) 352-0091

RADIOLOGICAL DEVICES PANEL

Voting Members:

Francine Halberg, M.D., Chair

Naomi P. Alazraki, M.D.

Judy M. Destouet, M.D.

Melvin L. Griem, M.D.

David Hackney, M.D.

A. Patricia Romilly-Harper, M.D.

James B. Smathers, Ph.D.

Temporary Voting Members:

Daniel B. Kopans, M.D.

Constantine Gatsonis, Ph.D.

Non-Voting Members:

Patricia Whelan, M.S.

Edward S. Sternick, Ph.D.

TABLE OF CONTENTS

P R O C E E D I N G S (8:40 a.m.)

Agenda Item: Call to Order and the Chair's Introduction - F. Halberg, M.D.

DR. HALBERG: I would like to call this meeting of the Radiological Devices Panel to order. I also want to request that everyone in attendance at the meeting to sign in at the attendance sheets, which are available outside the door.

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

At this time I would like all the panel members to introduce themselves and state their specialty, position, title, institution, and whether or not you are a voting member on the panel. I can start.

[Introductions were made.]

Thank you. I would like to note for the record that unfortunately one of our temporary panel members, Dr. Joseph Melton, was unable to attend the meeting today due to illness.

Mr. Monahan, would you like to make some opening remarks?

Agenda Item: FDA Introductory Remarks - John Monahan

MR. MONAHAN: Yes, I would like to note that I'm Jack Monahan. I'm the executive secretary for the Radiological Devices Panel. I'm a reviewer in the Office of Device Evaluation at CDRH. Today my primary interest is in trying to run a smooth meeting, so I hope that everything goes okay. If anyone in attendance has any problems or questions, please see me and I'll try to resolve them for you.

Before I begin, I would like to ask Dr. Yin, our division director, to say a few words.

DR. YIN: Good morning to you all. I am so pleased to have the privilege to present two plaques to two of our voting members that will be rotating off to become consultants to the panel. The first person is Dr. Hackney.

Dr. Hackney, it is my privilege to present this to you on behalf of our executive director. Thank you so much for serving on the panel.

It is my great privilege to present this to Francine, our chairman that has done so many difficult issues with us such digital mammography, bone densitometry, and many, many others, and especially today. Thank you.

You still will be our consultant, right?

DR. HALBERG: Thank you.

MR. MONAHAN: Thank you, Dr. Yin. As executive secretary, I also wanted to say it's been a pleasure to work with both Dr. Hackney and Dr. Halberg. We are going to miss them at the panel meetings, but they will continue to be consultants, so I'm sure that we will be calling on them periodically to help us.

At this point I would like to read a statement concerning appointments to temporary voting status granted by Dr. Bruce Burlington, director of the Center for Devices and Radiological Health.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990, and as amended April 20, 1995, Dr. Daniel Kopans and Dr. Constantine Gatsonis have been appointed as voting members of the Radiological Devices Panel for the November 17, 1997 panel meeting.

For the record, these individuals are special government employees and consultants to this panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review. They have reviewed the material to be considered at this meeting.

The following announcement addresses conflict of interest issues associated with this particular meeting, and is made a part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by panel participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interest, however, the agency has determined that participation of certain members and consultants, the need for whose service outweighs the potential conflict of interest involved is in the best interest of the government.

Waivers have been granted to Dr. Naomi Alazraki, Dr. David Hackney, and Dr. Melvin Griem for their interest in firms at issue that could potentially be affected by the panel's deliberation. The waivers permit these individuals to participate in all matter before the panel. Copies of these waivers may be obtained from the agency's Freedom of Information Office, Room 12A15 of the Parklawn Building.

We would like to note for the record that the agency took into consideration certain matters regarding

Drs. Naomi Alazraki, Constantine Gatsonis, David Hackney, Daniel Kopans. Drs. Alazraki, Gatsonis, Hackney, and Kopans reported interests in firms or matters not related to what is being discussed today. Since these matters are not related to the subject devices before the committee, the agency has determined that they may participate in today's deliberations. Therefore, the agency has determined that these individuals may participate in the panel's deliberations today.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants should excuse themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firms who products they may wish to comment upon.

If anyone has anything to discuss concerning these matters, you can advise me now, and we can leave the room to discuss them.

[No conflicts are noted.]

FDA also has a conflict of interest policy regarding persons making public statements at advisory panels. Dr. Halberg will ask all persons making statements either during the open public meeting or during open committee discussion portions of the meeting to state their name, professional affiliation, and disclose whether they have any financial interest in any medical device company.

I want to give you the parts of the definition of financial interest in this sponsor company. They include: (1) compensation for time and services of clinical investigators, their assistants and staff in conducting this study, and appearing at the panel meeting on behalf of the applicant; (2) a direct stake in the product under review such as an inventor of the product, a patent holder, or owner of shares of stock; (3) owner or part owner of the company.

No statement of course, is required from employees of the company.

FDA seeks communication with industry and the clinical community in a number of different ways. First, FDA welcomes and encourages pre-meetings with sponsors prior to all IDE submissions and PMA submissions. This affords the sponsor an opportunity to discuss issues that could

impact on the review process.

Second, FDA communicates through the use of guidance documents. Toward this end, FDA develops two types of guidance documents for manufacturers to follow when they are submitting an applicant. One type is simply a summary of the information that has historically been requested on devices that are well understood in order to determine substantial equivalents.

The second type of guidance document is one that develops as we learn about new technology. FDA welcomes and encourages the panel and industry to provide comments concerning our guidance documents.

Finally, I would like to remind you that the meetings of the Radiological Devices Panel tentatively scheduled for next year are the following dates: February 23; May 11; August 17; and November 16. Please mark these dates on your calendars. You must recognize, however, that these dates are tentative at this time.

I would like to turn the meeting back now to the chairperson, Dr. Halberg.

Agenda Item: Open Public Hearing

DR. HALBERG: Thank you. We will now proceed with the open public hearing session of this meeting. At this

time, public attendees are given an opportunity to address the panel to present data or views relevant to the panel's activities. Let me just mention that we would ask that the speakers in this portion of the session limit their remarks to about five minutes. If that is not sufficient, you can turn in any additional comments in writing to Mr. Monahan, and they become part of the public record for this meeting.

If there any individuals who wish to make a comment during this session, would you please raise your hand?

I don't see anyone who wishes to address the panel at this time. If that is true, then I will now close the open public hearing portion of this session.

Agenda Item: Open Committee Discussion - Charge to the Panel - Francine Halberg, M.D.

We will now proceed with consideration of the first of two PMAs to be discussed today. We can begin with presenters from Myriad. They will talking about PMA application P970026 for their SoundScan 2000 bone sonometer, intended to measure the speed of sound in the tibia.

I would like to request that the presenters from Myriad, the sponsor of this pre-market approval application set at the presenter's table, which is the table right up

there. After you have finished your presentations, I would also like to ask that you turn the table back to the FDA speakers who will follow you.

At this time I would like to introduce Barry Wyshogrod, Myriad Vice President for Strategic Programs, Technical Marketing and Regulatory Affairs, who will begin the company's presentation of the information contained in the PMA that we are considering today.

Mr. Wyshogrod.

Agenda Item: Myriad Presentation of P970026

MR. WYSHOGROD: Good morning, everybody. On behalf of all of us at Myriad Ultrasound I would like to thank the FDA for working with us during the past two years, and for bringing us in front of this panel today. To panel members, we thank you in advance for your time and for considering our product.

The following people are attending today on behalf of the company: two of our principal investigators, Dr. Robert Heaney from Omaha Nebraska, and Dr. Eugene McCloskey from Sheffield, England, our two regulatory consultants, Mr. Randy Beal(?), from the Boston area, and Dr. Ellie Orbach(?), from Israel, our founder, president and CEO, Mr. Alex Rappaport is here, and I am Barry Wyshogrod,

responsible for strategic programs, technical marketing, and regulatory affairs.

I apologize to some of you for my back.

Myriad Ultrasound is a small Israeli company. We began operations in 1991. We have developed our product over the years with the help of leading international clinicians and researchers. We have tried to adhere to the guidelines of the FDA, and have received excellent input and advice from FDA reviewers and staff.

The result is our SoundScan 2000, which was introduced in June 1994. Research began in 1992, and continues even today. As of now, there are over 300 systems in use worldwide in over 25 countries. The product is CE marked throughout Europe, and has received clearance from the Japanese Kasasho(?) authorities.

The SoundScan is our first and only product line. We hope to receive clearance for the United States, and to development enhancements on the product and other applications in the future.

The subject of today's meeting is our SoundScan 2000, PMA 970026. We are asking for clearance on the following four indications for use:

(1) that the SoundScan measures the velocity of

ultrasound, otherwise known as speed of sound or SOS in the tibia;

(2) that speed of sound through the tibia provides an index of bone strength, with stronger bone having higher velocities;

(3) that when compared to the results of a reference population of normal individuals, the SoundScan measurement provides a risk factor for evaluating overall skeletal mechanical quality;

(4) finally, that the SoundScan measurement provides information, which when combined with the patient profile and relevant risk factors, is useful in diagnosing or managing diseases associated with skeletal fragility such as osteoporosis, chronic renal failure, and hyperparathyroidism.

Following this introduction, Dr. Heaney will speak on the state-of-the-art of bone assessment and the SoundScan's role therein. I'll then describe the product and summarize our non-clinical and clinical studies. Dr. McCloskey will follow that with a discussion of the clinical utility of the SoundScan, and that will be followed by a short wrap-up.

At this time I would like to introduce Dr. Robert

Heaney. Dr. Robert Heaney is John A. Creighton University professor at Creighton University, Omaha, Nebraska. Dr. Heaney is a clinical endocrinologist, with an emphasis on bone biology and calcium nutrition, and with over 42 years of experience in the study of bone metabolism. Dr. Heaney has long has interest and involvement with ultrasound for bone assessment, and he was the senior author on the first multi-center trial of such a device back in 1989, with over 300 original papers to his credit.

We have asked Dr. Heaney to provide a brief background on bone assessment, quantitative ultrasound for bone, and to fit his own clinical findings with the SoundScan into this framework.

Dr. Heaney is being compensated for his time and travel. Dr. Heaney, please.

DR. HEANEY: Well good morning to everyone, and thank you for the opportunity to be here.

I would correct Mr. Wyshogrod on only one technical detail -- my university is being compensated for my time and travel; I am not. I received nothing from the sponsor here.

I am here really on behalf of the technology, rather than on behalf of Myriad. I worked with ultrasound

for a long time. I have had experience with several of the different devices. I'm satisfied that they provide the information which they claim to provide, and I am eager to get the technology more broadly approved in the United States so we can let utilization and market forces drive the inevitable improvements which we are likely to see.

Now if Dr. Melton were here with you this morning, it wouldn't be necessary to review some of this material, but I notice that none of you is a bone biologist, it may be useful if I review some things, which I'm sure you are familiar with, but may not be quite up to speed on.

First of all, I think we all recognize that osteoporosis is a problem of growing importance and severity worldwide. It is estimated that the cost to the U.S. in 1992 was about $15 billion -- something in that order of magnitude -- and that does not involve lost time. Those are direct medical costs.

The good news is that there is an increased availability of effective drugs, both for prevention and for treatment. Another division of this agency will be looking at the first of the selective estrogen receptor modulators at their panel meeting later this month. It is likely that that will be approved. So more and more effective

interventions are now and will soon be becoming available.

So it's important that we get tools out there to the practicing physician which will allow him or her to make choices about who might benefit from intervention. As much as the pharmaceutical manufacturers might like, we can't treat the whole population, so it is necessary to make some choices about who would be most likely to benefit.

Now the good news also is that the available tools are actually quite good; better than my cardiological and gastroenterological and other medical specialty colleagues have. That is because bone strength rises as approximately the square of bone mass density. So relatively small differences in bone mass make a big difference in bone strength.

As it turns out, a drop of one standard deviation in bone mass approximately doubles fracture risk. Again, your absent panel member, Joe Melton, a few years ago published a very nice analysis saying that if we could raise the density of the femoral neck by 10 percent, we would cut hip fractures in the U.S. by half. It's a very, very impressive size of an effect.

Now the question is, where is the best place to assess bone strength? If you are doing research, as my

center is, and if you are interested in a specific fracture, such as the spine or the hip, then the best place to measure is probably the spine or the hip, the place that you are most interested in.

But it turns out of course, that osteoporosis is a systemic disease, and if you have got decreased bone mass somewhere, you are likely to have it more or less everywhere. For that reason, if you are interested in global fracture risk, which is of course what the patient is interested in and what the physician is interested in, then it turns out that you can measure anywhere convenient -- hand, forearm, heel, spine, hip, total body; they all provide a good assessment of global fracture risk. They don't detect all the same people, because not everybody's bones are varying throughout the entire skeleton in perfect parallelism.

This has been the conclusion of all of the osteoporosis consensus statements that have been issued since 1987, so there is truly a scientific consensus from the field. If you want to pick up people who are at increased risk of fracture, then you can make a measurement virtually anywhere. Two sites are better than one, but in the practical order, one is what is going to be available to

most people.

In order to get widespread dissemination of this technology for the assessment of bone status, ideally the equipment should be low in cost; it should occupy little office space; preferably it should hang on the wall, like a sphygmomanometer. I don't think the device before us today is quite that compact, but some day it might be. Furthermore, the test procedure should be easily performed. It should require relatively little time, and it should pose low hazards to the patient or the operator.

The state-of-the-art today is dual energy x-ray absorptiometry, and of course with any tool there are pros and cons. On the positive side, it has high accuracy. As I say, higher than my radiological, gastroenterological, or cardiovascular colleagues have. We can measure our object of interest with higher numerical accuracy and precision than they can in theirs.

Secondly, it is very flexible. It allows an investigator to focus on many regions of interest. It is a premiere research tool.

On the negative side, it is expensive. It takes dedicated space that you can't use for something else that you have pay rent on year in and year out. It is

inaccessible for many people, because it tends to be located in big medical centers. It employs ionizing radiation, not much, but some, and because of that, and for many jurisdictions it requires a licensed radiological technologist to operate it.

Quantitative ultrasound has been around for a while too, although in this country mostly as a research tool. The quantitative ultrasound values which will be speed of sound or velocity and attenuation through a bone, in the types of patients we are going to be interested in mainly for this application, these values will be influenced predominantly by the mass density of the bone that is being measured.

Now bone texture and bone quality influence the ultrasound values to varying degrees, and later this morning Dr. McCloskey will show you some very interesting discordances between the density and the ultrasound value in patients with Paget's disease, and probably the same is true with patients with endstage renal disease, but the issue here is the detection of decreased bone strength, and most of that is going to be due to the change in bone density.

Thus, quantitative ultrasound is really functioning as a surrogate for bone strength. I say bone

density up here, but both bone density and bone strength are measurements of -- excuse me, both bone density and the ultrasound values through bone are surrogates for bone strength, and again, fortunately for our purposes, they both give similar risk gradients for fracture, so that one can be used more or less in place of the other.

This has been much the conclusion of large studies or major reviews that have been published in the last two years. The first I have listed up there is the large study of fractures project which is operated by Steve Cummings out of the University of California, involving nearly 10,000 elderly women.

The second is the Epidos(?) study from Europe. The third is the International Quantitative Ultrasound Consensus Panel. You see these have been published in the Journal of Bone Mineral Research, Lancet, or Osteoporosis International. The last is a major review of the technology, and the conclusion is just what I said, that the two technologies can be used virtually interchangeably.

Furthermore as I said, we have a tool that is pretty good. Whether we use BDM or quantitative ultrasound, as I have already indicated, a change of one standard deviation approximately doubles the fracture risk. But we

don't have such good indices for some other disorders. Blood cholesterol, one standard deviation indicates a 1.5 fold increase risk in myocardial infarction, and high blood pressure, a 1.3 fold increase in risk of cerebral vascular accident.

That doesn't stop us of course from measuring cholesterol or blood pressure, nor should it, but I simply want to remind you that we have better indices with respect to bone.

Now the usefulness, which Dr. McCloskey will develop in greater detail, is based simply on the fact that we need to select those can benefit from treatment. Furthermore, and I think this is a very important consideration, knowing what one's bone status is personalizes the issue, and takes a general well, I know I ought to do -- exercise more or take my calcium or go on estrogens or whatever the therapeutic intervention might be -- it personalizes it; makes it mine. Therefore, it's a very strong motivator. This has been shown in numbers of studies, for instance with smoking cessation, et cetera.

Although the application before you today does not speak about monitoring progress over time, this is also of course what physicians will be interested in ultimately,

when they have the technology available.

Now finally, since most of the devices that have been marketed or tested around the world have focused on bones that have predominantly trabecular structure, you might wonder why the interest in a cortical site. Well, actually the first ultrasound technologies were developed for cortical sites, in racehorses for example, et cetera.

The fact of the matter is 80 percent of our skeleton is cortical. All clinical fractures involve cortical bone, and more to the point, the clinical testing confirms that tibial ultrasound shows what you would want it to show, that is, it has got the expected decline with age that we know occurs with the use of other technologies.

It shows the expected male/female difference which accords with the bone mass difference in the two genders, and as the data that will be shown you later this morning demonstrates, it discriminates individuals with fracture as well, or better in some cases, as some of the other more established techniques.

With that, I thank you very much.

MR. WYSHOGROD: Thank you, Dr. Heaney.

This is the SoundScan 2000. It is a completely self-contained product. It includes an integral PC, all of

the analogue and digital ultrasound circuitry, and a printer for producing printed patient reports.

The SoundScan measures the velocity of ultrasound, otherwise known as speed of sound in the tibial cortex of the bone via what is called longitudinal transmission this way along the bone. Since the inception of the company several important questions have always been asked of us.

First, in general, does quantitative ultrasound really reflect the bone status? Second, is cortical bone specifically important to overall bone strength. Third, is the tibia a reasonable site to measure?

Now ten years ago there was not as large a body of evidence to answer these questions, but in the recent years and included within the PMA we cite over 50 published articles that confirm that the answer to these questions is yes. Now this by itself is not validation of the product, rather it provides a background or a framework into which the product fits.

The heart of the SoundScan is a unique measurement technology, a geometric array of piezal ceramic elements located within the transducer that measure the speed of sound longitudinally along the cortical layer of the bone, with immunity to the overlying soft tissue. The end result

is a measurement of speed of sound in the bone only, with no soft tissue error. Now that is the measurement itself.

For the clinical use, to identify individuals who may have decreased bone quality, we compare the reference, the results of the measurements to the population reference values which are included in the system. The system includes population reference values for men and women, and we will come back to discuss this later.

The output of a measurement is a patient report that looks just like this. All of the previous measurements are shown, as well as the most recent measurement, plotted against the population reference values and standard deviations. Numerically, the system reports the results of the speed of sound in meters per second, as well as the statistical T and Z scores.

The T and Z scores indicate by how many standard deviation above or below the population reference values is this person's measurement. The T score refers relative to the young adult people, and the Z score refers to the results relative to the persons own age.

There are no special installation requirements. Simply plug it in. It works on 110 volts. The system run using standard Microsoft Windows, and it includes a complete

patient file, which includes most of the risk factors commonly associated with bone disorders. The use of the patient file is completely at the clinician's discretion.

The system is what is called a dry system in that it uses no water. A measurement is made with three basic steps: identify and marking the midpoint of a tibia; applying standard ultrasound gel; and measuring. Measurement time is two to three minutes.

There is no calibration required, rather a daily verification is done using a supplied phantom. Now for the typical user, the result is a simple pass/fail go/no go result, and a graph that plots the last 100 phantom measurements so the user can see stability of the device over time. For the more sophisticated user, there is a Spreadsheet output of the last 500 phantom measurements for statistical analysis of stability.

Finally, minimal training is required. It takes about several hours to train an operator, and there is a learning curve of about 20-30 patients.

Finally, the product is safe. It uses no ionizing radiation. Its ultrasound output or acoustic power output is over 200 times lower than FDA limits. In measurements on 5,357 people in our clinical studies, there were no adverse

events. There were three complaints of static electricity. These were checked and found to be unrelated to the product.

That concludes the device description, and now let's move on to the non-clinical studies. The first of our four claims or indications for use is that the SoundScan measures the velocity of ultrasound in the tibia. It is the non-clinical studies which provide the formal validation for this claim.

First, the device has been proven to be highly accurate at 0.1 percent. This represents the mean error of measurements relative to the true correct value as measured on these materials. In our accuracy testing we used epoxy glass substraits. Epoxy glass has signal characteristics which are similar to those of a human bone given our measurement technology. The device is highly reproducible. At 0.1 percent, this is the coefficient of variation for measurements. Again, measurements were made on both epoxy glass and other substraits.

We verified and validated the fundamental design of the system using a variety of materials and including bovine tibia, and demonstrating that indeed the device has no soft tissue error. The accuracy and reproducibility in all of these tests are well within the specification of the

device.

Finally, using a variety of materials, but in particular bovine tibia, we demonstrate one of the expected characteristics given the technology, and that is that the speed of sound measurement is influenced in part by cortical thickness. Now this is important clinically, because it is known that one of the ramifications, one of the characteristics of aging skeletons and osteoporotic or disease skeletons is a thinning of the cortical layer.

The second of our four claims, that speed of sound through the tibia provides an index of bone strength, with stronger bone having higher velocities. Again, the non-clinical studies provide the validation for this claim.

Biomechanical testing of cortical specimens extracted from cadaver tibiae was conducted by Dr. Wilson Hayes and Dr. Mary Bouxsein from Beth Israel in Boston. The results here are shown for both tibial speed of sounds, and along side tibial BMD. The results demonstrate the very high correlations between the tibial speed of sound measurement and these mechanical characteristics of the bone -- the elastic modulus, the ultimate strength, and the yield strength.

This is perhaps the most important one of our

results from our non-clinical studies program, because it shows that SoundScan measurement is highly correlated to the mechanical strength of the bone.

That concludes our review of the non-clinical studies, and we move on to the clinical studies themselves. Our third and our fourth claims are clinical. That the SoundScan measurement provides a risk factor for evaluating overall skeletal mechanical quality, and that it is useful in diagnosing or managing diseases associated with skeletal fragility. The proof for these claims comes from the clinical studies.

The clinical studies program is developed around this fundamental thesis, that in order to demonstrate that the tibial speed of sound is useful clinical indicator of skeletal status, it is both necessary and sufficient to show that first, it provides accurate and precise results; second, that it behaves in a similar manner to other accepted assessments of skeletal status, particularly BMD insofar as it shows relationship to age, menopause, and gender; and finally and most important, that it can discriminate between patients with and without low trauma fractures in a comparable way to the other measures of skeletal status.

To validate this thesis we studied precision, correlation to anthropometric parameters, correlation to other established methods, in particular BMD, and we studied the discriminatory ability of these devices for fracture/non-fracture discrimination for both vertebral and appendicular fracture.

Six primary research centers were used in our studies; two in the United States, including Robert Heaney; two in Europe, including Dr. McCloskey, who will speak later; and two in Israel. A total of 5,357 people were studied worldwide.

This is the age distribution of the subjects studied. Our emphasis was from the ages of 20 to 90, with special emphasis on the peri- and post-menopausal years, those years associated with the low trauma fractures. In particular, in these decades note that we include close to 1,000, or over 1,000 people per decade.

Now let's begin to look at some of the results. The SoundScan measurement is precise. Within the PMA, we submit a variety of analyses on precision based on data from five recent centers, 10-97 people at each center, 192 people total, age 22-80, close to 500 measurements total. These represent healthy people, bone clinic patients, and

confirmed osteoporotics.

Tibial speed of sound has a coefficient of variation otherwise known as precision of 0.4 percent, as compared to densitometry and other quantitative ultrasound devices. When we standardize this number to take into account the population range and mean on over 4,000 people, we find that that standardized precision of the device falls within the range of BMD, and represents the superior end of the quantitative ultrasound device spectrum. This is a slight indication that our clinical findings should show that tibial speed of sound perform similarly to densitometry, and we'll see this later on.

To study the relationship between tibial speed of sound and anthropometric parameters, we first do basic correlation analyses. We present here the correlation on close to 4,000 people. I apologize for my description error here. We present the correlation data on tibial speed of sound and its relationship to age, years since menopause, and other anthropometric parameters.

For a comparison from the same population studied, we present the densitometry measurements that you see here. The overall result qualitatively shows that the correlation of tibial speed of sound to anthropometric parameters is

similar to the range observed in densitometry measurements, again indicating that we might expect to find that the clinical performance of tibial speed of sound is similar to that of densitometry.

Insofar as post-menopausal women have a higher rate of incidence of low trauma fractures than pre-menopausal women, we expect that characteristic also to be reflected in tibial speed of sound, and indeed it is. When we do linear regression on pre- and post-menopausal women at the various research centers, we find that the pre-menopausal slopes are all not significant, and yet the post-menopausal women decrease over time, with statistically significant rates of decline. This is based on data on over 2,700 women.

Insofar as women have a higher incidence of low trauma fractures than men, we look to see if that characteristic is reflected in tibial speed of sound. In over 4,100 people we show the results from the two centers that studied men versus women, and we find that men decrease in tibial speed of sound slowly over time, but at a rate that is about two to three times slower than their female counterparts.

Now we have often been asked about the

intertechnology correlations of tibial speed of sound to densitometry measurements, so we present the results for correlations for over 1,000 women. Tibial speed of sound has a weak to moderate correlation to densitometry measurements, but more important than that, tibial speed of sound correlation to densitometry measurement is quite similar to the intersite correlations of the BMD measurements themselves.

The two implications of these results are first that tibial speed of sound behaves similarly to densitometry, and second, that a measure of tibial speed of sound cannot be translated into densitometry, nor can a hip, forearm or spine measurement in densitometry be translated into another site.

Most important now, we come to what we call our discriminatory analysis where we choose fracture as a marker of impaired skeletal strength. The discriminatory analysis that we performed is based on an experiment whose objective is to measure the ability of the SoundScan to discriminate between patients with and without low trauma fractures, and then to compare that ability to that of bone densitometry.

We do this by recruiting various populations at the various research centers. We identify those people with

and without fractures, and we measure them with tibial speed of sound, and a variety of BMD measurements. Then we analyze and we evaluate the discriminatory ability of these various technologies and compare them using standard statistical techniques. The results that you will see will show the tibial speed of sound and bone mineral density show similar discriminatory abilities.

The discriminatory analysis was done on 2,057 women. These include 387 post-menopausal women with low trauma fractures of both appendicular and vertebral types. They are compared to 814 post-menopausal non-fracture controls and 856 pre-menopausal non-fracture controls.

The breakdown of these 2,057 women per research center is shown below.

Now I will put up the first of three slides that usually takes a while to get used to. This slide is meant to show the discriminatory ability between non-fracture and fracture groups. This slide shows the results for tibial speed of sound for each of the three research centers that studied this characteristic, which is a comparison of post-menopausal appendicular fracture versus pre-menopausal non-fracture controls.

Shown are the mean and standard errors for the

non-fracture cohorts, and the mean and standard errors for the fracture cohorts. I would like to just comment that on the next three slides that you will see, not every research center is shown, because not every research center performed every one of the discriminatory analyses.

In this characteristic, for these three research centers tibial speed of sound was a significant discriminatory of all of the research centers. The same picture is seen when looking at post-menopausal vertebral fracture also versus pre-menopausal non-fracture controls. But that by itself it not that instructive or enlightening, because it's not such a big deal to compare a 20 year old women to a 67 old woman.

So more important is the age-match data. So the next two slides summarize age-match data. For post-menopausal appendicular fractures versus age-matched non-fracture controls we show the results for tibial speed of sound on the left, and the available densitometry measurements from these centers on the right.

For all of the three research centers, tibial speed of sound was a significant discriminator between the non-fracture and fracture cohorts, and for comparison, at Dr. Heaney's center forearm BMD was a non-significant

discriminator.

Now if you are used to seeing those pictures, you are going to love this one. This is the test. This is the last of the discriminatory analysis slides of this format, and it compares vertebral fracture versus age-matched non-fracture controls for all of the research centers that studied this characteristic.

In four of the six studies tibial speed of sound is a significant discriminatory between the non-fracture and fracture cohorts. At two of the centers it is not, yet when we look at Dr. Heaney's results from the States, and compare densitometry measurements, we find that forearm BMD was also a non-significant discriminatory. When we look at Prof. Popovtzer's results from Israel and compare them to his densitometry results, again we find that not every densitometry site is always able to discriminate.

The net result of all of this data is that tibial speed of sound performs at least as well as densitometry measurements at all of the research centers.

Now another way to present the data is to use ROC curves. I don't expect you to read all the small text, but we put the curves on one slide so you could see the way the curves are shaped. What you are looking here are post-

menopausal women with fracture of either appendicular or vertebral types versus pre-menopausal non-fracture controls. The tibial speed of sound ROC curves are shown in bold. For every one of the research centers the areas under the curve are statistically significant. For most of the research centers the area under the curve is over 90 percent.

The other curves that you see are the other available measurements at the various research centers. They include forearm BMD, patellar speed of sound, and forearm, hip, and spine BMD. In every one of the cases tibial speed of sound performs at least as well as densitometry measurements.

Again, the more important test of discriminatory ability is age-matched analysis, so we present the first of two curves, two slides on ROC analysis for age-matched comparisons, post-menopausal appendicular fracture versus age-matched non-fracture controls. These are two representative ROC curves.

For some of the centers, like Dr. Heaney, tibial speed of sound has a ROC curve that is just like forearm BMD, yet in this study neither one of the curves were statistically significant. At other centers, the results are different. At other centers with different populations,

tibial speed of sound is a statistically significant ROC curve, with an area under the curve of close to 80 percent.

I would like to comment that because the populations at the various centers are not identical, we decided not to pool the data, and that is why we present the data for each center by itself.

This is the last of the ROC curves. It is the post-menopausal vertebral fracture population compared to age-matched controls for various centers. In all of the centers the tibial speed of sound curve behaves similarly to the other accepted methods. Not always was the area under the curve statistically significant as shown in the top two studies, yet in the bottom studies one sees statistically significant areas under the curve for every one of the technologies, and these include: hip, forearm, spine BMD, calcaneal speed of sound, and calcaneal BUA.

That concludes the summary of discriminatory analyses. Now we want to review the reference populations. The SoundScan includes reference populations for men and women. At present we include Caucasian values only. These were developed as per industry standards for inclusion and exclusion criteria.

The curves represent the means of population

reference values for women and men without fracture, and without the typical risk factors associated with bone disease. The curves include 1,207 women; 542 men. At present the system includes only the Caucasian reference values, yet we have a detailed protocol developed and Myriad Ultrasound will gladly welcome work with researchers in the States to develop reference values for other ethnic groups too.

In summary, we believe the data show that tibial speed of sound is a precise technique; that it behaves in a similar manner to the generally accepted methods of skeletal assessment insofar as its relationship to age, menopause, and gender are concerned; and most importantly, that it discriminates between fracture and non-fracture populations similarly to the accepted methods of skeletal assessment.

That concludes the summary of the clinical studies. I would like to just end with one comment on the issue of education. Tibial speed of sound, quantitative ultrasound, T scores, Z scores are all new to many clinicians in the United States. This means that it is incumbent upon both the companies and organizations like the FDA and the National Osteoporosis Foundation to develop guidelines and educational tools for physicians and patients

alike.

So within our labeling we have application notes which attempt to educate the physician about accuracy, reproducibility, and precision of the device, to explain the SoundScan measurements, and to address some of these questions on intertechnology differences that arise because the correlations between tibial speed of sound and densitometry measurements, and even between the densitometry measurements themselves is not equal to 1.

Finally, we are now undergoing review with the FDA on our second draft of a patient information sheet. This is intended to address most of the questions that we expect the typical patient to ask once these technologies come out onto the market.

That concludes the summary of our studies and device description. I would like to introduce at this point, Dr. Eugene McCloskey.

Dr. McCloskey is a senior medical research fellow at the WHO Collaborating Center for Metabolic Bone Diseases, which is headed by Prof. John A. Kanis, and affiliated with the University of Sheffield, and the Royal Haloshire(?) Hospital of Sheffield, England.

Dr. McCloskey has a longstanding interest in non-

invasive assessment of bone strength including densitometry and ultrasonic techniques. In addition to research, he is a practicing clinician involved in the day-to-day investigation and management of patients with metabolic bone diseases and particularly osteoporosis.

Dr. McCloskey has worked with almost all the major manufacturers of bone assessment equipment, and he has authored or co-authored over 75 publications in the field of bone metabolism and disease.

We have asked Dr. McCloskey to speak on the clinical utility of the SoundScan, and he is being compensated for his time and travel.

Dr. McCloskey.

DR. MC CLOSKEY: First of all, I would like to thank you for inviting me here this morning, and to say it is an honor for me to come and address you this morning. I was going to say it was an honor and a pleasure, but I'm withholding the verdict on the pleasure.

Just to hark back to what we were hearing from Dr. Heaney earlier this morning, as clinicians we have been nothing but impressed over the last ten years by the increase in our workload from osteoporosis. I guess one of the pleasurable things about this morning is the fact that

usually on a Monday morning I would be sitting in a large metropolitan bone clinic with about 40-45 patients with osteoporosis.

This burden of osteoporosis and fragility fractures a great task not only for health care providers, who have to cope with the problem, but also we shouldn't forget the patients who suffer a significant degree of morbidity from vertebral and appendicular fractures which to occur to them as a result of their skeletal fragility.

As we heard earlier, we are in the fortunate position that we have an increasing number of effective therapies available to us, including HRT and the newly developed serums, the biphosyhonates, calcitonin, calcium, vitamin D and so on, and this list is increasing steadily, so that we've got a great armory to reduce hopefully, the incidence of bone fragility fractures in the future.

But as Bob Heaney has said, and it is widely accepted that we can't treat everybody, and we need to target treatment to those at whom treatment is most necessary, and hopefully who will benefit the most.

I have been involved with ultrasonic techniques for about the last ten years or so. They have attractions as clinicians, because they have the potential to be

relatively inexpensive compared to some of the larger densitometric techniques that are available to us.

We are radiation-free. That's not a major problem with the current dose of radiation in equipment, but still you get some patients who are concerned about it.

The ultrasound techniques in general have potential to be mobile and more portable than densitometric equipment, and this will allow them to be placed within the community rather than hospital and research-based, and make the measurements accessible to a larger number of patients.

The standard approach that we take in the clinical management of patients is shown on this next slide. Basically, we have to start from somewhere, and certainly no argument in this country, and no argument worldwide for population screening to identify patients at risk of osteoporosis. So we depend either on the general practitioner or family doctor's awareness of risk factors within an individual, and increasingly individuals themselves are aware of risk factors that exist.

It has impossible to pick up a woman's magazine for the last ten years to read the problem page without having a problem about the menopause, osteoporosis and so on. So the women themselves are increasingly aware that

they may have a risk factor.

This risk factors include such things as: early menopause or prolonged amenorrhea, glucocorticol abuse, and respiratory diseases, rheumatological diseases, dermatology and so on; prolonged immobilization, and of course the existence of prior fragility fractures which may indicate that there is something wrong with individual skeletal strength.

So you present with the risk factors, and then you really want to have available to you an assessment of skeletal strength to aid in the management of the patient. So you can combine the risk factors with an interskeletal assessment, and that will lead to management decisions about what we should do in that particular individual.

Now in this next slide we have taken a series of 237 women who were invited to come along to our unit in Sheffield in England. Bob Heaney was saying England, Europe -- I said we are still debating about whether we're in Europe or not, but Sheffield, England. We identified a population of young, healthy women who are acting in this analysis as a control group. Within the 237 women we also identified groups of individuals who had risk factors that were on that list that I showed you earlier.

So we've got a total here of 18 women who have a history of steroid exposure; 8 with previous fracture; and 18 with a history of amenorrhea.

Now you can see here the women with steroid exposure are significantly older than the young, healthy population, and they have thereby a lower tibial speed of sound. You might expect partly that might be age-related, partly due to the steroid exposure.

The point is that if we had assessed the same individuals using spine BMD or hip BMD, then the mean reduction expressed as a T score from the young, healthy population is the same or greater using the tibial speed of sound than it is using the hip and spine BMD.

In the group with previous fragility fractures, again, they are slightly older than the younger, healthy individuals, but as you might expect, in these individuals who have had a previous fracture suggesting decreased skeletal strength, then the reduction of tibial speed of sound is so much greater, with a T score of -1.4, which compares very favorably with a T score of -1.6 and a T score of -0.9 if we had assessed them different than the hip bone mineral density.

In the final group we've got the amenorrheic

patients, and again the reduction that we assess these patients with tibial speed of sound, spine BMD or hip BMD all show similar degrees of reduction in bone strength as assessed by the variety of techniques.

So the technique of tibial speed of sound is giving us comparable data in a clinical sense in patients with risk factors to that which we would achieve using the traditional approach that we do using spine or hip BMD measurements.

This is going to go on to give you three case histories to illustrate how we can use tibial speed of sound in a clinical setting. The first one is a 75 year old lady who presents with a history of glucocorticoid use for a total of seven years following a diagnosis of polymyalgia rheumatica and temporal arteritis, and again, that is a significant risk factor, systemic use of steroids, and she sustained a fractured wrist in 1989, suggesting that she did have a degree of skeletal fragility.

You have two approaches as a clinician in this case. One is to say I'm convinced this really is enough evidence of skeletal fragility. I'm going to treat her anyway. But it's a bit analogous to saying, I'm convinced by looking at the records of your face or the fact that you

get headaches that you get high blood pressure, and I'm going to treat you anyway.

So it's nice to have some assessment of blood pressure or skeletal strength. We measure her tibial speed of sound, and she comes out with a T score of -3. That is in the same ball park that we see in patients in the cross-sectional studies with prevalent vertical fractures, and we know that she has got skeletal fragility. It confirms our suspicions, and she is a good candidate for intervention to prevent further bone loss.

The next illustration is a 55 year old lady. This lady was rather on the obese side, with a long history of back pain, including several periods of confinement to bed for a total duration of several months between the ages of 30 and 38, with prolapsed disk and spinal degenerative disease.

So she had a history of immobilization. At the age of 53 she the removal of non-functioning tumor with replacement therapy, but had gone through the menopause at 49, and this probably wasn't of relevance to her bone status, but she also gave a family history of previous fragility fracture, and although it was not in a first degree relative, her maternal grandmother, that still rings

small alarm bells.

She undergoes tibial speed of sound measurement. She has a tibial speed of sound of 4,207 images per second. That takes her well into the upper echelons of the young, female healthy population, and with the experience that we have had with the tibial SoundScan over the last five years, we knew that that was going to compare very favorably with what spine BMD and hip BMD would tell. The recommendation is that this patient can be reassured that there is no need for intervention.

As clinicians we like to make decisions based on the maximum amount of data that we feel we need to have to be comfortable with management decisions, because we are going to put patients on drugs that have side effects, that have interruptions to lifestyle in taking them, and so on. So we need to be convinced ourselves so we can convince the patients to improve compliance and so on.

This is illustrated in the final case that I present, a 47 year old lady, who in her thirties had a two and a half year history of amenorrhea, which was thought to be stress related. She subsequently went on to have an early menopause at the age of 42 years. She was using a Becotide(?) inhaler for several years for asthma, and again,

there is great debate still about whether inhaled steroids and systemics have as much detrimental effect as systemic use of steroids.

She had a first degree relative with a history of fragility fracture. Her mother had fractured her arm. She is a peri-menopausal lady. We undertook a tibial speed of sound measurement, and she comes out with a T score of -0.8, and that is tending towards the level that we get slightly nervous about in peri-menopausal women, because this is the ideal prevention group, but I was still not convinced with just one measurement. I need something else to help push me through the door, deciding whether to treat or not.

So she undergoes hip bone mineral density assessment, spine bone mineral density assessment. The hip bone mineral density assessment gives a T score that is identical to her tibial speed of sound, the -0.8 T score. Her spine score which is measured by the same densitometric technique on the same day, she was a T score of -1.8.

This apparent discrepancy between the sites comes back to what Prof. Heaney was saying earlier, that it is something that as clinicians we are quite well used to dealing with. It is quite fortunate that patients have a single blood pressure and a single cholesterol level, but we

know that you don't have a single bone mineral density. But if you are low in one place, you are highly likely to be low in another. Because of this spine score tipping the balance, treatment was recommended for this individual, in combination with her existing risk factors.

So that gives you some idea of the clinical utility. Prof. Heaney had mentioned earlier that there is great interest as to what exactly measurements such as speed of sound are measuring. It is quite clear from all the data that you have seen and patients with fragility fractures and predominant osteoporosis, that the relationship between speed of sound and bone mineral density is very comparable in what they tell us about an individual's skeletal status.

Paget's disease is a different kettle of fish altogether, and for those of you who are non-clinicians or non-radiologists, just a brief recap on Paget's disease. It is very common in the north of England, where it's one of the Paget's capitals of the world. Paget's disease is a disease of the elderly where you increase in bone size, bone thickening, and a disruption of collagen architecture within bone. If you look at an x-ray of Paget's disease, the characteristic thing you want to see is an increase in bone size to discriminate it from other sclerotic diseases.

We undertook in ten patients who fortunately, or unfortunately for the individuals had got Paget's disease of one tibia, and a normal tibia on the other side, which allowed us to undertake measurements of bone mineral density and ultrasound velocity or speed of sound in both the normal and Pagetic tibia.

On the left here we've got the results of the bone area, which is derived from the DXA measurements. You can see that compared to the unaffected side, the area of the bone was about 1.2 standard deviations higher than the unaffected limb, so it is increase in bone size. The bone density was about one standard deviation higher in the affected limb than in the normal limb.

In contrast, the tibia speed of sound was almost 4 standard deviations lower in the affected than in the unaffected limb. What do we derive from this? The first thing we derive is that they are measuring different things within the bone. What do they tell us about bone strength and Paget's disease? Well, we knew the Paget's disease is associated with an increased risk of fragility fractures. It's a well recognized, well established complication of Paget's disease.

So in this particular instance the speed of sound

is telling us something perhaps of more clinical utility than the DXA measurement, but that just an illustration of some of the potential differences between speed of sound and bone mineral density. I think if we hark back again to all the data that is contained within the PMA and patients that we see routinely in the clinic, the performance characteristics are very similar.

So I would just like to summarize by saying that having shown you the data in Paget's disease, we can certainly say that speed of sound is not just a direct measure of bone mineral density, but that both speed of sound and bone mineral density are surrogates for skeletal strength, and that is what we are interested in measuring.

In the patients that we see who include the clinics with fragility fractures and diseases other than Paget's disease, there is a close correlation between what we learn from changes in bone mineral density, and changes in tibial speed of sound.

Obviously we are concerned about the performance of the techniques, but over the five years of experience with the SoundScan, we found that the performance in terms of precision, in terms of the relationship between the precision and its population variance, and its ability to

discriminate between patients with and without fractures compares very favorably with the use of bone mineral density measurements.

I'd like to conclude there. Thank you very much.

DR. HALBERG: Thank you.

At this time do the panel members have any questions?

MR. WYSHOGROD: Just one more thing.

DR. HALBERG: I apologize. Go ahead.

MR. WYSHOGROD: I just want to summarize with this one wrap-up slide. We made four claims or indications for use for our product. The first two relates to the fundamental technology, and we believe that the data for accuracy, reproducibility, no soft tissue error, and our sensitivity to cortical thickness data confirms that in fact we are measuring what we expect to measure, speed of sound in the tibia.

The second claim is a very important one to us, index of bone strength. The biomechanical testing confirms that in fact the speed of sound measurement reflects the bone strength.

The third and the fourth claims relate to the clinical use of the device. We said that the SoundScan

provides a risk factor for evaluating overall skeletal mechanical quality. We believe that the precision data and the comparison to the other accepted methods, specifically densitometry, vis-a-vis the performance relative to anthropometric parameters and intertechnology correlations, and most importantly discriminatory analyses confirms that in fact we have a skeletal mechanical quality evaluation tool.

Finally, we make a claim that the device is useful in diagnosing or managing disease associating with skeletal fragility such as osteoporosis. Of the 1,200 women that are included in the age-matched analyses that you have seen, 387 of these women had post-menopausal low trauma fractures. By the traditional clinical definition, these women are osteoporotic. Therefore, we feel justified in claiming that the measurement is good for discriminatory ability for osteoporotic patients.

We also mention chronic renal failure and hyperparathyroidism. I just want to mention that although we don't have time to review the results in today's presentation, within the PMA is data on over 300 people, chronic renal failure patients, limited number of data on hyperparathyroid patients and HRT user data. For all of

these groups, tibial speed of sound is a significant discriminator between the diseased and non-diseased patients, and between HRT users and non-users.

We hope that you will agree with our findings, and we thank you very much for the time and for the consideration of our product.

Thank you.

DR. HALBERG: Thank you again. Dr. Kopans?

DR. KOPANS: First of all, I'm not an expert at all in this field, but I just had a couple of questions. It was mentioned that the thickness of the cortical bone makes a difference in sound transmission. Given that the tibia is, in a simplified version, a cylinder with varying thickness through the wall, how does the device keep you from angling through that wall, so that you are actually going through an apparently thicker portion of bone, as opposed to perfectly perpendicular to the cortex?

MR. WYSHOGROD: In fact, the speed of sound when the signal impinges upon the bone, impinges actually on a wide range of angles, and it travels in various directions. The way in which the system is designed, we're actually picking up the fastest moving signal that moves through the bone. That turns out to be the one that goes longitudinally

along the bone, and that is a bulk wave through the bulk of the cortical layer.

So it is not that we are oriented specifically to one particular angle and the angle is not that critical. We will always pick up the signal of interest to us.

DR. KOPANS: But I thought you said that it was related to thickness.

MR. WYSHOGROD: One of the factors. One of the factors that influences the bone other than the issues of quality and density and elasticity is the thickness. The thickness comes from the fact that the bottom wall or the bottom end of the cortical layer sets what is called a boundary condition. That limits the speed of sound so that as it gets thinner, the speed of sound is moving through the bulk way. It sees that bottom boundary, and slows down.

DR. KOPANS: I'm sorry for being dense about this, but if the transducer was angled at an angle to that boundary layer, which the inner layer is also a circular, ovoid layer, wouldn't it be sending sound through a thicker -- an apparently thicker area?

MR. WYSHOGROD: It does. You're right, it does. The first signal that comes to the receiving section of the transducer is the one that goes down and propagates through

the bulk of the layer. There are other reflections going on, and other waves are set up in the other directions, you are right, but the ones that interest us, and the first one that is received by the transducer is the one along the path of interest to us.

DR. KOPANS: Is that that it's through the thinnest layer? Is that a way to think about it?

MR. WYSHOGROD: Well, it's through the bulk, with an influence by the bottom boundary condition. The bottom boundary condition is the thickness of the wall, among other factors.

DR. KOPANS: I had one other question. Dr. McCloskey, in the data that you presented, and I understand that is just a very small fraction, the numbers for the young women who presumably had normal bone density and those with previous fractures, the confidence intervals were overlapping, so those weren't statistically significantly different. Maybe Dr. Gatsonis would want to comment on that.

DR. MC CLOSKEY: That is a well recognized phenomenon within the whole field of densitometry and ultrasound. We don't get complete separation. There are not sort of truly diagnostic tests in that sense. They are

risk factor for fragility factors, rather than a truly diagnostic test. We have much better ways of diagnosing fractures; one would do just a simple x-ray. We are not trying to diagnose fractures from the measurement, and you do get some overlap.

DR. HALBERG: Perhaps along those lines, I just wanted to ask for a little bit more elaboration on the ability to discriminate between women at higher risk for vertebral body fracture, as opposed to appendicular fracture. In a similar way, there seemed to be much more overlap in the two groups, with vertebral body fracture as opposed to appendicular fractures. If you could just common on that, and elaborate on that. I know Dr. Heaney's data didn't seem to show the same ability to discriminate.

MR. WYSHOGROD: Overall when one looks at the data, you are right, the vertebral speed of sound has a slightly higher sensitivity to discrimination between appendicular fracture/non-fracture than vertebral fracture/non-fracture. You see that when you look at the ROC curves you will find more statistically significant and wider separation between the fracture and non-fracture cohorts. That is true.

Nevertheless, the overall performance for both the

appendicular and the vertebral fractures still matches that of densitometry techniques even though yes, the technology seems to favor the appendicular type of fracture. There may be some explanations for that, that relate to what is being measured. The cortical bone that we are measuring may reflect sites in the body that have a higher percentage of cortical bone content.

Indeed, although I didn't mention it, when we do analyses on our correlation data between tibial speed of sound and other densitometry sites, indeed we find that the highest correlation on the body is between our measurement on the tibia and forearm BMD, which happens to measure the site that is predominantly cortical bone also.

So there seems to be a slight predisposition of the technology to favoring sites on the body that have the higher cortical concentration.

DR. HEANEY: I would like to stress that the purpose of our study was primarily to get population-based normative data. We had a county near Omaha that was enumerated by our epidemiologist, and we took a random sample of individuals from that enumerated county, particularly people over age 50, which is what our primary study was concerned with.

We had a basically healthy population. We were not a bone clinic. We did not have patients coming to us with bone disease or with osteoporosis. As a matter of fact, in that entire county in our enumerated sample, there were only two or three people with a clinical diagnosis of osteoporosis.

So we had a healthier group overall. We've got a better idea of what the population normative values are then perhaps you could get with a volunteer bias walk-in clinic situation. The fractures we had ascertained, were ascertained all by history. A post hoc determination was made blindly as to whether they were low or high trauma fractures. This is a farming population, and it included not being in a tractor that rolled over, or falling off the barn roof, or other such situations, where it was relatively easy to assign that fracture to a high trauma basis.

I think overall we have a different population, different study, different criteria for fractures. You cannot easily make comparisons between them. Even so, in our group we did find a clear discrimination for appendicular fractures of low trauma type.

DR. MC CLOSKEY: I think if I can just add one more comment to that. It is pretty easy on most x-rays of

most radiologists looking at x-rays to define appendicular fractures, whereas there is a huge literature over the last 10 years, and I spent -- some people might say wasted -- three years of my life deciding what is a vertebral fracture on an x-ray, because if it is a gross crush factor, 100 percent will agree. If it is a normal vertebral, 95 percent will agree, and there is a large gray area in between.

It depends on the threshold that you use to define what is a vertebral fracture as to your ability to discriminate between patients with and without fracture will appear. So that is an issue that is not yet fully resolved.

DR. GRIEM: I wanted to ask Dr. McCloskey, have you looked at any monophasic(?) Paget's where it's just the destructive phase that occurs?

DR. MC CLOSKEY: No, we haven't had the opportunity to do that. The patients that we have had available to us were all long-term, predominantly sclerotic phase disease patients, and we haven't got the opportunity. We are doing some follow-up studies following biphosyhonate therapy to see whether changes induced in bone mineral density and tibial speed of sound, but we haven't got that data analyzed yet.

DR. ALAZRAKI: When we do bone mineral density

conventionally, we usually have either or both spinal and hip measurements. We know that in older women, and in older patients in general that the spine is often not considered accurate because of the presence of osteoarthritic degenerative changes, and even fractures in vertebral spine can either send the BMD up or down.

Therefore, we usually rely upon the hip measurement more in the elderly. So I was curious if you compared your bone mineral density, and presume that lumped the hip and the spine, to your speed of sound in post-menopausal women. Do you have the hip bone mineral density versus the speed of sound?

DR. MC CLOSKEY: We separate our spine and hip bone mineral density, and we have looked at the discrimination using spine and hip bone mineral density, and we have looked at the correlations between tibial speed of sound and spine and hip bone mineral density. As you quite rightly say, spine bone mineral density is fraught with problems in elderly individuals. It is our policy in Sheffield not to do spine BMD measurements in women over the age of 65 precisely because of that issue.

DR. ALAZRAKI: The data that you presented here for the company showed the comparison between bone mineral

density, which was a conglomerate of the spine and hip measurements.

DR. MC CLOSKEY: No, on the table I had shown --

DR. ALAZRAKI: No, I think it was Barry who showed it.

MR. WYSHOGROD: This comes back to the issue of the intertechnology correlations. Let me just spend a minute on that. I think that generally people would agree in the medical community that if one is interested in the fracture risk let's say of a particular site on the body, one should measure that site. So if you have a particular interest in the hip, you should measure hip; or spine, you should measure spine. I'm not sure that all studies support that, but I think that generally that's the accepted guideline.

Now when we start looking at all of these other new technologies and peripheral sites of measurement on the body, one of the things we find in our data is the same result that Dr. Harry Genant presented three months ago at the Hilogic(?) Sahara panel meeting.

That was that he tried to answer the question of if we identified women that had low BMD at one site, and then measured the same group of women with another

technology, how many of these women would fall from one group into the other and vice versa, which is what most of the clinicians want to know. He cited 60-80 percent.

Sixty to 80 percent of the women who would fall low as measured by one technology, will fall low as measured by another technology. Within our data, when we look at that characteristic, we also find the same type of performance.

That means that if a person comes into a clinician's office and gets a measurement with one of these devices, statistically the changes that their skeleton will be assessed, and that the doctor will identify people at risk with lower skeletal strengths will be the same for all of the technologies when one considers the propensity to fracture of all sites. If one wanted to measure any one site on the body, then that should be measured with direct site measurements.

That hinges back and relates to the intercorrelation results that we presented before. A measurement of tibial speed of sound cannot be translated into grams per square centimeter, nor can it be translated into the results that one would obtain at another site on the body.

What it says is that a person has a generally weaker or stronger or average skeleton, and that is statistically the same kind of performance as BMD. But one should be careful -- and this is in our educational tools -- one has to be careful not to translate results from one measurement to another, or attempt to predict the results of another site on the body using a different site measurement.

DR. ALAZRAKI: But what I was referring to was your claim that the speed of sound tibial measurements are as good or better I believe you said, than BMD in identifying those post-menopausal women without osteoporosis.

MR. WYSHOGROD: Right, and the reason is that in fact, and the statistics show that it is.

DR. ALAZRAKI: But what I would like to know is if you separate out the BMD hip measurements, which is what we really use in those post-menopausal women, how does the speed of sound then compare in identifying osteoporosis or women with fractures?

MR. WYSHOGROD: Do you want to answer?

DR. MC CLOSKEY: We have looked at this in a large elderly community-based population in which we have hip BMD measurements and tibial speed of sound measurements in

combination. We didn't do spine BMD measurements for the reasons I have stated earlier.

We had forearm BMD. We had heel ultrasound. We had metacopal(?) morphometry. We had a whole variety of techniques to look at skeletal strength in these individuals. The gradient of risk for prevalent vertebral fractures was highest with hip BMD, followed next by tibial speed of sound, and forearm calcaneal measurements came in with lower odds ratios.

DR. HALBERG: Dr. Gatsonis.

MR. WYSHOGROD: I would like to just comment if I may. I would like to put this one slide back on. This is the slide for the discriminatory analysis of post-menopausal vertebral fracture versus the age-match non-fracture controls. You will notice for example that if you look at Dr. Genant's data from the United States, that happens to be on an osteoporotic only population.

Tibial speed of sound, hip and forearm BMD are all significant discriminators. So in other words, when we start taking a look at each particular technology or site, in that case spinal BMD is not, but one shouldn't jump to conclusions on that about how it works all the time, because if one looks for example at Prof. Popovtzer's data from

Israel on the right, you will notice that hip and forearm BMD in that case were not significant discriminators, but spine was for vertebral fracture.

That is why overall all of the technologies and the sites of measurement on the body are really statistical, and one really has to be careful to drawing conclusions that any one measurement works all the time for all types of fractures. Both of the technologies have false positives and false negatives. The data basically shows that the overall performance of all of the measurement sites is the same.

DR. HALBERG: Thank you. Dr. Gatsonis.

DR. GATSONIS: I just wanted to ask a couple of questions about the ROC analysis. It seems that if I understand finally why you call this a risk factor versus some kind of a diagnosis device, because you are not looking at it as a diagnostic device. Nevertheless, you do use ROC analysis where the outcome is fractures.

It seems that what you are trying to do in the ROC with that analysis is to see how the device helps over and above other kind of predictive factors, for instance age, for instance menopausal status, et cetera. Hence, to look at differences between pre-menopausal women and post-

menopausal women and so on is not really relevant. You pointed that out in your evaluation.

When you go then into a stratified analysis, in other words, you stratify women by menopausal status and so on, you see that: (a) the answers are different across your various studies, and (b) the discriminating power is not as strong as of course when you are looking across strata.

Do you have an explanation as to the variability that has been observed across studies, number one. Number two, if I wanted to think of a patient cohort in which I would use this device and find really important clinical results, which of these studies has that kind of patient cohort, and why don't the other studies have that patient cohort?

In other words, I have a hard time understanding for what patient cohort I would be using this sort of scanning device.

MR. WYSHOGROD: First of all, let me start by answering in the beginning. As I mentioned, the different studies include different patient populations. We see the characteristics of some of the patient populations reflected in the results that we have seen in the data. In other words, some of the studies are clinic-based patients, and in

those we see lower fracture cohorts, with fractures having lower speeds of sound. We see rates of decline with age that are lower than in the general population and so on.

I think that at this point it would be a little bit hard for us to define specifically on which particular patient populations the device should be applied, though our general feeling is that the data confirms that the discriminatory analysis behaves similarly to densitometry. Therefore, those people who normally today would be sent for densitometry measurements, could be sent alternatively for ultrasound measurements.

There is not enough data on large enough populations to say that this is a screening tool, and that is why it is not a screening tool, and it shouldn't be used for that right now. What it should be used for is at a clinician's judgment, those people on whom there is some suspicion or question about their skeletal status. This provides another risk factor. It is a piece of the puzzle. It is a not a sole determinant of somebody's propensity to fracture. It is simply an additional measurement.

Because of its characteristics though, it is an additional measurement that could be used instead of densitometry. As Dr. McCloskey pointed out, there are some

times when it should be used in addition to densitometry or vice versa, because you then get more pieces of the puzzle that is the jigsaw of the person's overall skeletal strength picture.

DR. HALBERG: Thank you.

DR. GATSONIS: In terms of the densitometry, I didn't you present a form of statistical comparisons on these populations. With pair designs, this is what densitometry said, this is what SoundScan said and so on. Is that fair? Did I understand you right there?

DR. MC CLOSKEY: You understood that correctly. This is an issue that just doesn't impinge on tibial speed of sound. It impinges on the whole technologies for every skeletal site in the body. As clinicians we are well used to the fact that if you open the Pandora's box and measure everybody at every skeletal site, you will get a different result at every skeletal site. That applies to all the technologies.

So basically one measure of skeletal status is much better than none, and you have to use what you've got available to you. I would feel less happy with -- we've shown in studies that measurements on the mandible are useful in the systemic skeletal disease. So one measure of

health of skeletal status is useful.

There are again, the guidelines that are being developed and are not really fully in place yet for DXA measurements and their clinical utility. There is no reason why such similar guidelines could not be applicable in goodness of time to ultrasonic techniques.

DR. HALBERG: We need to move the discussion on. Perhaps Dr. Heaney and Dr. Destouet, and then we'll move on to the FDA.

DR. HEANEY: I would like to elaborate on Dr. McCloskey's comment. Conrad Johnston and his colleagues a number of years ago at the University of Indiana showed that if you take all of the non-skeletal risk factors, that is age, history, body build, fair skin, all of those risk factors and put them all together, you get a predictor of bone mass, but a very, very weak one.

A much, much stronger predictor was by directly measuring bone mass either with densitometry or in this case by ultrasound. When the technology becomes cheap, then it becomes relatively inexpensive to make the measurement directly, rather than guessing at it by looking at what somebody looks like.

DR. DESTOUET: This is for Dr. Heaney. I'm not

sure what the rate of bone turnover is in cortical bone as opposed to trabecular bone. One of the claims by the manufacturer is that we could follow these patients after some therapeutic intervention. My question is then at what time interval do we follow them to expect a significant change in tibial speed of sound? How good would that measurement be in helping the clinician manage that patient?

DR. HEANEY: The bone turnover rate in cortical bone will vary site to site, just as it does in trabecular bone. We could go off into an elaborate side discussion here. I'm sorry about that, but at my 1990 presidential address at the Copenhagen conference, I told the conferees that I thought this pursuit of trabecular bone was misguided, and that it wasn't really an important issue, that the region of the body was much more important.

There are some trabecular areas that don't turnover at all, and other cortical areas that turnover quite rapidly, but on average the annual turnover rate for cortical bone is about 4-5 percent, and for trabecular bone it can be as high as 20-25 percent per year, so there's a big difference between then.

That then gets to your question about how often should you do repeat measurements. We don't have those

kinds of data for tibial ultrasound, so I can't answer for that technology specifically, but for the field in general, for the types of patients we are dealing with, for the most part you won't see perceptible changes in individuals at intervals much less than two years. Now there will be exceptions to this, but the problem is the measurement error, even as good as it is, will often be larger an appreciable change within the individual.

So I counsel physicians note to waste their patients' time or delude themselves by taking measurements much more often than every two years; maybe one year in some cases. People with a very large, active disease, kind of like a high turnover anemia for example, you can see changes very quickly, but if you have got an apathetic skeleton, it is not going to change very rapidly. So you have to make these clinical judgments.

DR. HALBERG: Thank you very much.

Let's move on to the FDA presentation. Dr. Ewa Czerska will be the FDA's review team leader for PMA 970026. She will provide an introduction to the PMA from the FDA's perspective.

Agenda Item: FDA Presentation of P970026, PMA Overview - Ewa Czerska, Ph.D., M.D.

DR. CZERSKA: My name is Ewa Czerska, and I am the review team leader for SoundScan 2000 by Myriad Ultrasound Systems.

The document was reviewed thoroughly by Food and Drug experts for engineering, physics, tox/biocompatibility, software, biological/sterility, labeling, clinical, and statistical aspects. Several questions were asked, but they were answered by the company. There are still some outstanding questions, mostly about labeling, that are going to be discussed later on with the panel. There are still some tests that we are awaiting the results from.

SoundScan 2000 is a pulsed ultrasound device to assist the clinician with skeletal evaluations. It measures the velocity of ultrasound passing through the human tibia. It calculates the speed of sound along the defined longitudinal distance in the cortical layer of the tibia. The results are expressed in meters per second, and are also presented as T scores, which are units of standard deviation rated to reference population values, and Z scores, eight matched controls.

The SoundScan consists of the ultrasound transducer, a single unit sending and receiving acoustic signals to and from the patient's tibia; the electronic unit

consisting of a computer and ultrasound unit; verification phantom to simulate human bone for daily verification. Here I would like to add that it is a small, portable device which is important, in the care of osteoporotic patients that are frequently immobilized.

The transducer -- that is a picture of the transducer -- is positioned in the midpoint of the tibia, halfway between the apex of medial malleolus and the distal apex of the patella. The ultrasound then is sent by the transducer and measured by the same single unit.

The next show will the details of it, and that might also answer some of Dr. Kopans' questions. There is a transmitter in the head of the transducer that is emitting ultrasounds which are subsequently measured over the defined distance between the receiver one and receiver two. This is a 5 centimeter distance.

Before the measurements are done, there are two depth finders also contained the transducer head that are measuring the depth where the cortical layer of tibia is present. Soft tissue was not an issue that has been proven by non-clinical tests.

Those are Myriad's indications for use that have been already discussed by the company. SoundScan 2000

measures the velocity of ultrasound speed of sound in the tibia. Speed of sound through the tibia provides an index of bone strength, with stronger bone having higher velocity.

When compared to the results of a reference population of normal individuals, the SoundScan measure provides the risk factor for evaluating over all skeletal/mechanical qualities. The SoundScan measurement provides information, which, when combined with the patient's profile, and relevant risk factors is useful in diagnosing or managing diseases associated with skeletal fragility such as osteoporosis, chronic renal failure, and hyperparathyroidism.

At the end of my presentation I would like to show to the panel that recently was discussed, Sahara bone sonometer. This SoundScan differs from Sahara. It measures speed of sound as opposed to Sahara measuring speed of sound and broadband ultrasound attenuation. It measures speed of sound in bone cortex. It doesn't measure the trabecular part of the bone. The bone that it is based is the tibia, while the Sahara measures the calcaneus.

At this point I would like to introduce Dr. Sacks, our clinical reviewer, who will discuss the clinical review of this device.

Agenda Item: Clinical Studies - William Sacks, Ph.D., M.D.

DR. SACKS: Good morning to the panel. When I finish, I will make a comment in answer to Dr. Kopans' question, because I understand the point exactly that he is making. We'll come back to that, but let me finish my prepared presentation first.

There will be a certain amount of redundancy in this, and I will try to get through it as quickly as possible. When we get to the next device, you are going to appreciate the redundancy very much, because of the complexities.

First of all, just to stress the only meaningful clinical endpoint in the field of osteoporosis is the ability of bone to resist fracturing. Now cortical thickness and porosity, which are reflected by the device's measurements of speed of sound are the main determinants of cortical strength.

Now the microarchitecture of the cortex also contributes to its strength, and Dr. McCloskey talked about how that shows up for example in Paget's disease, but interestingly there is no significant change in non-Pagetic bone with just age, and therefore that does not contribute

particularly to the decline of strength of bone with age.

Now the company has shown in its bench testing that the speed of sound along the tibia varies with both the porosity of the cortex and also with its thickness as long as the wavelength of the ultrasound beam is at least as great as the thickness itself -- a point that may not have been made earlier -- when it is at least that long, and the wavelength is chosen so that it is longer than the usual range of cortical thicknesses in the tibia. Then the cortex happens to act as an acoustic wave guide.

Actually, I suppose this is as good a point as any to make that point. I think what Dr. Kopans is asking is when the device is placed on the tibia, if it is tilted right or left, as opposed to up or down. What we saw in the slide that Dr. Czerska showed was that there are depth finders that keep the device from tilting up and down, but the side to side tilt, when you think of the cross-sectional area of the tibia as a cylinder, is the thing that is problematic.

However, it turns out that the tibia is not of course a cylinder. It happens to be more triangular in its outer shape. The inner shape tends to be circular. The device is used on the medial tibial plane, which is fairly

flat. You can feel it on yourself. It has got very little soft tissue over it. There is no muscle, it is just skin and fat and connective tissue.

That tends to stabilize the placement of the device, one. Two, in the training of the technologist there is a learning curve in which multiple measurements can be made, and you can look for the one that gives you slightly, that is the thinnest cortex, because the slightly speed of sound is in fact reflected. The thinner the cortex gets, the slower the speed of sound in the tibia.

So I think those things can -- I think that was an excellent question. I think those things are part of just the technologist making sure that he or she has the minimum figure.

The point that Barry Wyshogrod made it had to do with the tipping in the other direction, and that is that the sound goes in, it fans out, and it is the fastest arriving signal at the far end that has to do with the fanning in the sagittal plane of the device.

Now cortex and trabeculae play different roles in different kinds of fractures. The cortex is much more protective when we are dealing with bending fractures or spinal fractures. These are more the kinds of fractures you

see in the appendicular bones. Whereas in the vertebral bones, compression fractures are the most common. There cortex and trabeculae play a roughly equal role in protection against such fractures.

Now the company has shown that the tibial cortex declines in strength with aging, similar to the decline in trabecular strength throughout the body. Measurements of bone by DXA necessarily include both trabecular and cortical bone, though in varying site-specific proportions.

Nevertheless, DXA shows a similar decline of mass in each skeletal site with age, so it is reasonable to expect just as heel measurements indicate the status of other body sites, that measurements of declining tibial cortical strength should give some indication of the decline of cortical strength throughout the body.

When these considerations are combined with the relative proportions of cortical and trabecular bone at the various skeletal sites, it is reasonable to expect that measurements of tibial speed of sound be approximately as good an indication of susceptibility to vertebral fractures as heel sonometry, and perhaps better for appendicular fractures.

Now we have seen before, and I will go over this

just very quickly, there were six sites, two in the U.S., the rest abroad, with the number of subjects as shown there. Our statistician, Mr. Dawson, has gone over the statistical results, and as the company has said, they did not pool these results, and deal with them individually, but the results were statistically significant.

Without spelling out the details center by center, the clinical endpoints that were looked at in the overall set of studies -- and I've got these in the order of importance -- (1) the ability to discriminate fracture from non-fracture populations; this was done retrospectively in these studies; (2) the precision of the device; (3) the relationship of the speed of sound to age, menopausal status, and gender; (4) young normal reference values, (5) lastly and least importantly I think for our purposes here is that the correlations with DXA or BMD measurements were also studied.

Now this gives an idea of which centers studied which types of fractures. As you can see, only the Liberman study did appendicular age-matched fracture discrimination. As has already been pointed out, the matching of elderly women with fractures to young normals is really of no significance whatsoever, since it is of such great

significance statistically, though it has no clinical significance.

These are age-matched fracture discriminations. So the Liberman study did look at the appendicular, and indeed vertebral sites both, whereas most of the other centers -- all but Ziegler's in Germany -- looked at vertebral fractures. All but Liberman's looked at precision. All but Liberman's looked at age, gender, and menopausal status. As far as their reference populations are concerned, there were three of the centers -- Dr. Heaney's, Dr. Ziegler's, and Dr. Liberman's.

Now in terms of the safety and effectiveness, as has been pointed out, the device is without significant risk. In particular, it involves no ionizing radiation. It is fast. It is without discomfort to anyone who can lie on their back, and therefore we can concentrate on the issues of effectiveness.

First, as I said before, the studies at all centers were retrospective, and the age-matching of women without history of low trauma fracture to those who did have low trauma fractures was done appropriately by our statistical review.

Looking at the results from the various centers in

terms of appendicular fracture discrimination and vertebral fracture discrimination, you can see the NS stands for non-significant. We had a number of not statistically significant results. Those have to do with the small numbers.

To concentrate, however, on the ones that did have the statistical results, Dr. Liberman's study being the largest, did have statistical significance looking at the area under the curve. That is what AUC stands for, for the ROC curves. ROC standing of course for receiver operating characteristics.

He got an area for the appendicular fractures of 0.78 and for the vertebral fractures of 0.75, again, referring to the fact that as we might have expected and I alluded to earlier, that the cortical features do tend to discriminate between appendicular fractures, which involve bending or spiral fractures, more so than vertebral, but that is of course, probably not a statistically significant difference between these areas. It is just suggested.

Drs. Kanis and McCloskey in England also got a significant result of 0.69, an area under the curve for just vertebral. They didn't study the appendicular.

Let me make a couple of other comments before we

get to this. The company did demonstrate that speed of sound had a coefficient of variation of about 0.4 percent. This is a more precise measurement than broadband ultrasound attenuation to begin with. Since this device only looks at speed of sound and not at the combination, such as the heel sonometers do, it can be expected to have a smaller coefficient of variation or a greater precision. The 0.4 percent should be compared with values of about 1-3 percent for the heel sonometers and DXA devices.

Thirdly, the studies did demonstrate, as previously mentioned, that the tibial speed of sound does decline with age, and indeed it does decline faster in women than in men. That parallels other measurements of bone.

Lastly, the databases of the young normal Caucasian women in Liberman's and Ziegler's studies in Israel and Germany were essentially the same as for Dr. Heaney's population in the United States with respect to both the means and the standard deviations of the tibial speed of sound.

Therefore in summary, first, the device measures tibial speed of sound. This does reflect decline of cortical thickness, and increase of cortical porosity both, and these are both universal features of aging.

Secondly, the thickness and the porosity of the cortex do determine it strength.

The device discriminates retrospectively age-matched populations with and without low trauma fractures, though specific appendicular sites were not examined separately in these trials, that is hip versus wrist and so on. They were just lumped together, which is reasonable considering that as I think Dr. Heaney pointed out, that a woman is more interested in whether or not she is at risk for any fracture, and therefore I think that's appropriate.

Fourthly, the coefficient of variation, as I stated, is 0.4 percent, which is lower than that of heel sonometers and DXA.

Lastly, it is safe, fast, and causes no particular discomfort.

DR. HALBERG: Thank you. Mr. Monahan?

MR. MONAHAN: We're going to take a break now for about five minutes before the panel begins their discussion.

[Administrative remarks.]

[Brief recess.]

DR. HALBERG: I'd like to call the meeting back to order. Before we proceed with the review and discussion of P970026, Mr. Monahan will remind panel members of their

responsibilities in reviewing today's pre-market approval application for SoundScan 2000.

MR. MONAHAN: I would like to remind public observers at this meeting that while it is open to public observation, public attendees may not participate except at the specific request of the chair.

The medical device amendments to the Food and Drug and Cosmetic Act enable FDA to obtain a recommendation from an outside expert advisory panel on medical device PMAs which are filed with the FDA. We are asking you to make a recommendation concerning whether this PMA should be found approvable, approvable with conditions, or not approvable. A recommend must be supported by data in the application, or by publicly available information.

Your recommendation may take one of three forms. You may recommend that the PMA supplement be approved with no conditions attached to the approval.

You can recommend that the PMA supplement be found approval subject to specified conditions such as resolution of clearly identified deficiencies cited by you or by FDA staff. Examples can include resolution of questions concerning some of the data or changes in the draft labeling.

You may conclude that post-approval recommendations should be imposed as a condition of approval. These conditions may include a continuing evaluation of the device, and submission of periodic reports. If you believe such recommendations are necessary, your recommendation must address the following points: the reason or purpose of the requirement; the number of patients to be evaluated; and the reports required to be submitted.

You may find the application not approvable. The act, Section 515B2(a-e) states that a PMA can be denied approval for any of five reasons. I'll brief remind you of three of these reasons that applicable to your deliberations and decision. The three are: there is a lack of showing of reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the labeling.

To clarify the definition of safe, there is a reasonable assurance that a device is safe when it can be determined based on valid scientific evidence that the probable benefit to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use outweigh the probable risks.

The valid scientific evidence used to determine the safety of the device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.

The PMA may be denied approval if there is a lack of showing of reasonable assurance that the device is effective under the conditions of use prescribed, recommended, or suggested in the labeling.

A definition of effectiveness is as follows. There is a reasonable assurance that a device is effective when it can be determined based upon valid scientific evidence that in a significant portion of the target population the use of the device for its intended uses and conditions of use, when accompanies by adequate directions for use, and warnings against unsafe use will provide clinically significant results.

The PMA may be denied approval if, based on a fair evaluation of all the material facts, the proposed labeling is false or misleading.

If you make a non-approvable recommendation for any of these stated reasons, we request that you identify the measures that you believe are necessary, or steps which

should be undertaken to place the application in an approvable form. This may include further research.

I will turn the meeting at this point back to Dr. Halberg.

DR. HALBERG: John has already reminded us that while public observers of the meeting are open to observe it, that public attendees may not participate unless specifically requested to do so by the panel. I was wondering if Mr. Monahan would present the discussion questions to the panel.

Agenda Item: Panel Deliberations

MR. MONAHAN: Let me first read the discussion questions, and then I will put transparencies up so that they are viewable to everyone as the discussion proceeds.

1. We have asked the panel today to discuss whether or not they believe that the PMA contains sufficient data to conclude that the SoundScan 2000 can discriminate between post-menopausal age-matched women with and without low trauma fractures, both appendicular and vertebral.

2. We also want the panel to discuss the labeling of the device, including the indications for use, and whether or not they are appropriate given the data provided in the PMA with reference to the following:

a) Should fracture risk assessment be included in the indication for use statement;

b) Should a statement be included that data on the risk of a specific appendicular site fractures has not been provided; and

c) Are there other recommendations regarding items that should or should not be included in the labeling for this device?

3. One final catch-all discussion is, are there any issues not fully addressed in the PMA which might require post-market surveillance or a post-market study?

DR. HALBERG: I will just remind the panel members that you also have a written copy of the questions in the folder.

The first point, do the panel members feel there is sufficient data in the PMA to conclude that SoundScan 2000 can discriminate between post-menopausal age-matched women with and without low trauma fractures, both appendicular and vertebral?

DR. GRIEM: Yes, I think so in that I was not assigned this question, but the reviewer was assigned this question was ill.

DR. HALBERG: Dr. Melton, right?

DR. GRIEM: Yes, but he, I think, concurs.

DR. HALBERG: Indeed he does. I have his review.

Any other discussion? If not, let's move on to the second question.

Dr. Alazraki?

DR. ALAZRAKI: Perhaps the point that I would like to ask about is in a way indirectly related to the question we are discussing right now, but I would like clarification on the very excellent precision results that the instrument appears to have of 0.4 percent.

What I would like to just clarify is, was that precision based on multiple operators using the instrument, or if someone could review exactly how they derived that number.

MR. WYSHOGROD: That number represents an intraoperator, single operator precision figure. That has become, at least within this industry, a standard or a specification for the products. Within the PMA, as I mentioned, there is more data on a variety of different precisions, interoperator precision, that is, several operators is 0.6 percent. Intersystem precision between different systems coming off the production line is 0.4 percent. So that spans basically the range of the precision

performance of the device.

I also just want to comment again, people should keep in mind that the reason that we present standardized precisions is to factor in the population ranges and means so that overall people have a good feeling for what these devices can do in the clinical setting.

DR. ALAZRAKI: Then one further question about that. It was sort of discussed a little bit earlier, and that is that although the FDA pointed out that it is not as important to them how this compares to bone mineral density, in a sense I think there is some importance; for us to discuss that a little bit.

One point that I would like some clarification about is in general in bone mineral density I believe the precision limits the valid repeatability of the test in terms of how much time is reasonable to recommend a repeat test. This precision is much better than bone mineral density precisions. Are we then limited by the physiology of tibial bone turnover in terms of when it is reasonable to do another test?

DR. HEANEY: Mr. Wyshogrod presented standardized coefficients of variation. Now a standardized coefficient of variation simply takes the range of values you are likely

to find in the population that you will be using, and then takes the precision and refers it to that.

If I recall his presentation correctly, that was about 3 percent, not 0.4 percent. But the same is true with the bone density measures as well. You may have a density averaging say 1.0, but it never goes all the way down to 0. That is, the dynamic range you are likely to find in a population is only a fraction of what those values are.

In order to compare one procedure with another, you have kind of got to look at the measurement precision as a function of how broad the dynamic range of the measurements will be. What you see with ultrasound is that it is as good as bone mineral density, and tends to be at the better end of the spectrum at those precisions.

Is that an adequate answer?

DR. ALAZRAKI: Yes, that clarifies a lot.

DR. HALBERG: Any other discussion about this point?

DR. GATSONIS: On the evidence that was presented here showing that the higher risk under the ROC. It seems that there are two studies that show this, and there are two studies that don't. The two studies that show this is the study by Kanis and the study by Liberman. The ROCs even

there are quite different from other.

I just want to make sure that I understand that the patient selection for the Liberman study was such that the people that ended up having fractures were not more severe let's say, than what you would find in a normal population when you have a fracture and so on.

In other words, I am concerned that this is not the usual prospective cohort evaluation of a diagnostic test because of the various choices that have been made about the patients that entered into this particular study. I am concerned that these results may not be generalizable despite the fact that they are very large. As far as I could read through the information here, I did not see that level of explanation and detail.

DR. HALBERG: Would you like to address that?

MR. WYSHOGROD: The patients in the Liberman study basically represent a broad range of the population. That data comes from over 3,000 measurements of women throughout Israel. They come from a variety of sources that range from community centers to volunteers to nursing homes to companies and volunteers and so on. So that data represents probably among the broadly ranging populations that we have studied.

The patients are prospectively chosen in that we know nothing about them. When they come into the study, they just volunteer and they are measured. Those are the results that we find from there.

DR. GATSONIS: How do you assess the presence of fractures on them?

MR. WYSHOGROD: In that particular study, on history. All other studies --

DR. GATSONIS: So for that particular study, which is the largest study, you did not have radiologic confirmation?

MR. WYSHOGROD: Right, that is correct.

DR. MC CLOSKEY: The study that we carried out in Sheffield was based on four general practice lists in Sheffield and three of the towns around Sheffield. The patients were invited by letter of invitation sort of at random from the lists. The minimum age was 75 in the study, and the rate of recruitment was similar to all studies in that age group of population. All patients underwent measurements and had two lateral spine radiographs, and were practice diagnosed by a semiautomated morphormetric lateral spinal viewgraphs.

DR. ALAZRAKI: One other point of clarification.

The large study from Israel, did that limit the participants to Caucasians, or were there also other groups in there?

MR. WYSHOGROD: No, that study is Caucasian only.

DR. HALBERG: Okay, should we move on to the second discussion point? Perhaps I will just read this again.

Please discuss whether the labeling of this device including the indications for use are appropriate given the data provided in the PMA application with reference to the following:

a) Should fracture risk assessment be included in the indications for use statement;
b) Should a statement be included that data on the risk of specific appendicular site fractures has not been provided; and
c) Are there other recommendations regarding items that should or should not be included in the labeling for this device?

Actually, I had some concerns about the labeling, and actually would like to use Dr. Melton's review to discuss this as well. I think that all of us who are interested in osteoporosis evaluation are really interested

in assessing fracture risk, and that perhaps that should be addressed in the indications for use.

One of Dr. Melton's points was he was a bit confused about the term -- what I think I would like to do for this part of the discussion actually is put up the indications for use labeling, and perhaps start with that and how we think that -- and perhaps comment on that.

DR. GRIEM: In the contraindications there is also a statement, "Insufficient data exists to determine whether the velocity of ultrasound in the tibial cortex has any value in independently predicting eventual fracture."

DR. HALBERG: There was that statement in the PMA. There was also Dr. McCloskey's comments today in his statement in the written materials which stated that SoundScan measurements provide an indicator of skeletal fragility, and consequently a future fracture risk.

I thought that perhaps we could: (a) clarify that; and (b) address one of the points Dr. Melton made. That was that he found the term "skeletal mechanical quality" in the seventh line down somewhat confusing. I had actually had a strawman revised indications for use to put up. I thought maybe could move towards that and see what the panel thinks about changing the indications for use that

they use the wording of Dr. McCloskey and Dr. Melton.

Could we put up a different indications for use statement? I think panel members probably have the original indications for use statement on page 5 of Section 3, if you would like to flip back to the original one.

What this does is it deletes "evaluating overall skeletal mechanical quality," and substitutes skeletal fragility for that, such that the third sentence reads: "When compared to the results of a reference population of normal individuals, the SoundScan measurements provide a risk factor for skeletal fragility."

The next sentence starts out the same. "The SoundScan measurement provides information which when combined with a patient profile and," I inserted the word "other relevant risk factors, it may be useful in managing osteoporosis as an indicator of future fracture risk."

The points that were raised in Dr. Melton's review are that it is premature to speak of diagnosing osteoporosis until diagnostic criteria have been proposed. He felt that managing would be a better term. He also thought it was confusing to list osteoporosis with chronic renal failure, hyperparathyroidism, et cetera, since the later are usually considered secondary causes of osteoporosis.

That is basically what I took and put in up there. I thought that perhaps I will ask the panel members to comment on this indication for use statement.

DR. ALAZRAKI: I wonder whether it would be appropriate to include in there that when compared to the results of a reference population of normal individuals, we are really talking about normal Caucasian individuals.

DR. HALBERG: I think that would be very appropriate to put in there. In fact, it's critically important to put in there.

DR. DESTOUET: Dr. Halberg, it was pointed out that because of the rate of bone turnover in cortical bone, that in managing osteoporosis we should have another paragraph that should state that follow-up evaluation of tibial SOS should be performed at a certain period of time, whether it be two years or whatever, indicating that the follow-up evaluation in managing these patients may not change within a year or so or six months. There are some patients who come back for repeat evaluation.

I'm not sure where to put that, but at some point we need to indicate that the management of these patients must include the change in cortical bone turnover.

DR. HALBERG: I agree that we need to put in

something along those lines. My concern is that there was virtually no data presented on follow-up studies, and therefore I'm not sure that we should actually have follow-up guidelines in an indication for use, but let me ask other panel members.

DR. ROMILLY-HARPER: My suggestion would be maybe in the warnings and contraindications saying that insufficient data exists as the adequate time.

DR. HALBERG: It should be perhaps no more often than every two years.

DR. KOPANS: I guess I would like to pick up on what you were saying about useful in managing osteoporosis. That suggests to me that there are follow-up data, and that it is a way of measuring whether your therapy is successful. I would suggest somehow changing the maybe useful managing osteoporosis, to maybe useful in the evaluation of an individual for osteoporosis, and leave managing out until they are data that show that it is useful in managing.

DR. HALBERG: I agree with that. Other comments? I think evaluating is really the key.

DR. GRIEM: There are some other contraindications, and that is obesity, leg edema, and all of this sort of thing in Section 3, page 8. The question is

if a person has varicose veins of the leg and the technician doesn't place the transducer in the right place, how much does that change the outcome? Their in vitros suggest that overlying soft tissue is not a problem, but we don't have any data when we have this as a contraindication about obesity.

DR. HALBERG: Yes, I had that down as one of my concerns also. Could anyone address the issues of obesity and pretibial edema, and why that was listed as a potential contraindication, and what the data are?

MR. WYSHOGROD: The reason that that was put in, in general was just as a guide to clinicians on the use of the device. There is a small percent of patients were the leg is endemic or swollen where the measurement cannot be executed, and the operator knows that, because the machine simply will not execute the measurement.

This is not a case where the result is a wrong result. It is a case where the measurement could not be made. So we felt that we put it into the labeling of the device so people would just be aware. In the early days of the device when people didn't know that at our clinical research, sometimes they would spend ten minutes trying to measure a person who could not be measured, until we came

and told them that when you see that within a few seconds you can't take a reading, this person falls into that category, and that is why that notice is there, and that's what it is for.

DR. GRIEM: Well, this really brings up the whole question of the instructional guide that the technician has, and whether these sorts of things shouldn't be included. I think a thorough history of previous fracture for instance, and you bring this up as a contraindication. I think these are all important in guides to the technical team that is ultimately going to use this device.

MR. WYSHOGROD: I would like to comment that these issues are included in the training program. The device is intended to be used after individualized training. This is done now worldwide either directly by us, or by our representatives. We believe that the device, especially at this point in the introduction of what is a relatively new technology to the field of bone assessment, that individualized training is important.

So within our training program this issue of how to measure and when to know when you are in trouble, and when you can't make successful measurement, that is part of our training program.

DR. HALBERG: Thank you. Dr. Hackney?

DR. HACKNEY: I'm concerned that the new indication may overstate the data that is available. Although everyone is interested obviously in fracture risk, we don't have any prospective data for predicting fracture risk with this. We have data that correlates speed of sound and patients who do or do not have fractures.

I'm not sure if I read this indication, I would realize that this is based on only that data, and on no prospective data, since if the intended use is to take someone who doesn't have a fracture and see what the likelihood is that they will get one later on.

By the same token even if we take out the word "managing," I still think that people are going to do serial scans in patients unless they are told that there is no data to support the change in speed of sound in response to therapy. Unless we give people that information somehow, either by toning down this wording, or by adding that information in, I think this reads as if we have a technique that is known to predict fracture risk based on a prospective study, and a technique whose change over time in response to therapy has some data, and we don't have any.

DR. HALBERG: Do you have a suggestion for

changing the wording?

DR. HACKNEY: Well, when we talked about evaluation, I might say initial evaluation, in addition to taking out managing, and that may give us an idea. I'm still concerned about saying it as an indicator of future fracture risk unless we add another statement that says, although there is no prospective data to support this use.

I'm not sure what to do with it, but I think leaving it as is makes it sound much stronger than I would be comfortable with.

DR. HALBERG: Maybe the FDA can work with the company on that.

DR. MC CLOSKEY: I think this change of the statement should be noted as coming from one of the panel members, from Dr. Melton, who is a renown world authority in this field. While the lack of prospective data is acknowledged by all, there is a large body of evidence that when we started getting into bone density measurements in the early days of ultrasound, cross-sectional studies were the way in which these techniques were assessed.

The good news was that we got around to eventually doing the long-term prospective studies, the gradients of risk that we had seen in the cross-sectional studies were

comparable to those that were demonstrated in the prospective studies. I think it's that knowledge that Dr. Melton has probably used in this thoughts behind this, to change the indication.

DR. HALBERG: I might add that this is me paraphrasing Dr. Melton. So I want to be fair to him.

DR. HACKNEY: I think we would be perfectly reasonable to recapitulate that argument, and say that we are extrapolating from other results, particularly bone mineral density to make us think that this should work as well. But that is different than implying that perhaps the prospective data is in hand.

DR. HEANEY: Just to amplify on Dr. McCloskey's comments, not only do we have prospective fracture data for BMD, but we do for ultrasound; not with this device, but we do for ultrasound at the patella. That has been published. That is only a few centimeters up the leg, so it's not an unreasonable extrapolation.

DR. ALAZRAKI: I was going to say that if we accept that the measurements are accurate indicators of osteoporosis, then we have to accept that we're also talking about predicting fracture risk, because that is what it's all about. Otherwise, we don't need to know if a patient

has osteoporosis. It's almost part of the definition in my opinion.

DR. KOPANS: I have the same set of concerns that have been express. How put in there may be an indicator of future fracture risk? It sort of dilutes the message, but at the same time I think it is accurate.

DR. ALAZRAKI: By everything we know, it's an indicator of future fracture.

DR. GATSONIS: Well, I presume you could say nothing about that in the sense that if anybody knows about osteoporosis, this says something is useful in initial evaluation of osteoporosis. You could stop there, because there is no other evidence to suggest either management or indicator of future practice as a matter of empirical study.

DR. HALBERG: So is the sentiment of the majority of the panel that we should address the issue somehow of skeletal fragility, perhaps with a good set of qualifiers -- excuse me, the risk for fracture, or that we should not?

DR. SACKS: Let me just throw one other thing in here. It is more a question I guess for Dr. Gatsonis, but for the panel as a whole. We have been looking at retrospective as essentially in one important way, equivalent to prospective data on fractures. If you simply

consider that when you take a point in time and you make measurements with the population that makes up those who have had fractures, are simply looking backward in time, for a short period of time, perhaps in the last couple of years.

We have been treating that as about as good an indicator as what is likely to happen in the next couple of years. There is of course a difference in that in the previous years the women were younger than they are going to be in the next couple of years. Furthermore, that the rate of fractures will increase as you go on.

But it isn't that different an animal. There are similarities and differences, and I just wanted to mentioned that, and also just to remind everybody that of course what we are dealing with here is only one of any number of risk factors of all kinds of other clinical measurements, and this is just thrown into the mix. I thought Dr. McCloskey's presentation that gave several different clinical examples makes that fairly clear. So I just want to throw that out for further discussion.

DR. MC CLOSKEY: I think it seems a little bit meaningless to have a measurement that we do today which is associated with skeletal fragility if we don't aptly extrapolate that to what it means for the future. We are

making decisions to treat patients to reduce what we think is going to happen in the future. So I think we are not interested in treating osteoporosis just for today. The patient is worried about the future.

DR. HALBERG: Dr. Alazraki, do you have any comments?

DR. ALAZRAKI: I'm just trying to reconcile this discussion with the wording of the labeling. I think what we are hearing here is that yes, we accept that the SoundScan measurement provides information, which when combined with patient profile and other relevant risk factors can be used to indicate osteoporosis.

I think we can say although which specific data for this system were not available, but which conventional knowledge indicates is useful in managing osteoporosis and as an indicator of future fracture risk.

DR. HALBERG: So basically this statement with a few more qualifiers?

DR. ALAZRAKI: With a few more qualifiers, and also the lack of data about the timing.

DR. HALBERG: The qualifiers including the data.

DR. ALAZRAKI: Or exactly how it should be used.

DR. HALBERG: Let me suggest that we throw out Dr.

Alazraki's suggestions, and that we leave it to the FDA to do the exact wordsmithing, but that we have the spirit of the indications for use statement now.

DR. ALAZRAKI: I have one other thing that I would like just some clarification about, and perhaps some discussion if you think it is warranted, to know whether or not we ought to be saying anything about the relationship between bone mineral densitometry measurements and this. In the real world many, many, many women out there, and men and other patients with particular problems which lead to osteoporosis have had all kinds of measurements done by bone mineral density.

The translation of those measurements to this -- we do not know. What we would not like to see is for a number of patients, for their next scan or their next procedure to get this, which is not translatable to that. So I'm wondering whether there shouldn't be something in there, although it probably would be part of the company's educational materials, I'm not sure everybody gets the package indications from the FDA. Not necessarily will they always have the company's educational material, although I hope they do, and I compliment the company for that.

DR. HALBERG: Mr. Wyshogrod, do you wish to make a

comment?

MR. WYSHOGROD: We agree wholeheartedly with what you said. That is why this issue is discussed in the physician labeling and in the patient information sheet. That is supplied then with every product that goes out the door to everybody.

In general, I agree that on an educational level on the part of organizations such as the FDA and the NOF, et cetera, this has to be also addressed by them, and we'll gladly work with the organizations, and here the Office of Women's Health also, because the educational issue and answering the questions that you raise is very important to the proper use and understanding and acceptance of these new technologies.

DR. HALBERG: I just want to underscore the importance of that. I think up until now bone mineral density evaluation has been in the hands of physicians who really understood the limitations of the technology. Now this is a machine that will probably go into small medical offices in rural areas, into the hands of physicians who really may not understand that this test is not absolutely predictive for any one woman. I think that has to be a very important part of the physician education materials.

DR. ALAZRAKI: One other point of clarification. You describe the Z values and T values just the way bone mineral density does, but you haven't really translated those traditional T value cut offs that the WHO or the NHANES trials have described to be used in the definitions of osteoporosis. What can you tell us about that?

MR. WYSHOGROD: First of all, you're right, this is an important issue. Within the application notes that are now included in the PMA for the proposed labeling of the device, we include some general guidelines. They are not guidelines. It's more a summary of the data that you have seen presented today. It is the one time where we actually allow ourselves -- and we make a note of it -- to pool the data together to summarize a picture of fracture/non-fracture discrimination. We provide that and we say this should be used just for general information for the clinician.

There are no set guidelines today for quantitative ultrasound yet. That will happen probably in the years to come, just as the WHO definitions came into being for densitometer. There is no doubt that it will take a few years before this comes into play.

As a company, we think it is going to be very

difficult for us to define to a clinician hard and fast cut offs. We would like to stay away from that. We just think it's not our responsibility. We don't have enough data.

We do feel that the consensus organizations and the ultrasound standardization committees will address these issues, and will have to address these issues in the coming years as not only ultrasound comes into the use clinically, but as the variety of different ultrasound manufacturers come out with different sites of measurement and different parameters, education again will come into play, and cut offs will be developed over time.

DR. HEANEY: Once again, I think we are all sorry that Dr. Melton isn't here. I thought it was of considerable interest in what you quoted from him, Dr. Halberg, that until agreed upon definitions of osteoporosis can be reached -- Dr. Melton was one of the co-authors of the WHO paper which defined those limits. Obviously he doesn't think that that is the last word in osteoporosis diagnosis yet.

DR. HALBERG: No, he does not.

DR. HEANEY: The field is very schizophrenic. Is it a value on a bone mass measurement, or is it a condition of skeletal fragility? The Copenhagen consensus conference

redefined osteoporosis for the first time in a century of as condition of skeletal fragility due to decreased bone mass and microarchitectural deterioration of bone tissue, but the consequent increase of risk in bone fracture. I know it by heart.

It's a long definition, but it's got everything in there that you need. It's not a handy thing that you can remember very easily. Low bone mass is really a risk factor for osteoporosis. Low speed of ultrasound or low attenuation are risk factors for osteoporosis, because they are all surrogates for that fragility issue, which we can only measure destructively, and of course we can't do that in our patients. You can't break their leg to see how strong it is.

DR. HALBERG: Thank you.

Should we put up the third discussion point? Are there any issues not fully addressed in the PMA which would require post-market surveillance or a post-market study? Does anyone here feel a need for that?

DR. GRIEM: It would seem to me that we need additional evaluation of populations from cities like Chicago or New York, where you have African Americans, orientals, Hispanics, many of whom have American Indian

blood. These populations need to be evaluated for the United States.

DR. ALAZRAKI: Yes, I agree. I'm sure that that has to be one of the priorities in terms of what the company has to do. Also, I think with FDA's encouragement -- and I'm not sure that we need to require that as a post-market study, and it is in the best interest of everyone, the company, included to get their data and follow-up with these T scores, and as close as you can get to the border, this is it for this group, the fracture rate increases by such and such when you get to this point. I am sure they are going to do that. It's just something which perhaps the FDA ought to say, we expect that.

DR. KOPANS: I'm a newcomer to the panel, so if I'm out of line, tell me so. I am surprised in picking up with what Dr. Gatsonis was saying is that a prospective analysis of a device isn't a requirement. I understand the rationale and the fact that it would have to be I suspect, a huge study. Again, I don't know the mechanism, but I would love to see a prospective analysis of the study, with the endpoint being subsequent future fractures in some kind of future trial. I don't know if that is something that is done with these processes or not.

DR. HALBERG: I think with those comments in mind, would anybody like to make a move for approval, approval with conditions, or a denial of approval? Does anyone want to make that motion?

DR. GRIEM: Well, I would like to move for approval, but there are a couple of other points I would like to make. It seems to me that the method of calibration and the general way the machine is used day by day needs to be clarified, enhanced, and so forth. The technician should be able to reproducibly gather the data.

There is this work station. What are the system checks on the electronics, and are there ways of checking the software and hardware? There is an analog to digital converter in the device, and a reduction in voltage on the analog side of that could change the data.

It seems to me that one needs to look for bad cables, spot computer failure, and the rest, and that there should be a daily verification system and a quality assurance device that is more than 500 patients. I think are the instructions clear enough for the instruction manual, and I didn't have those.

Should there be a log book to allow for quality assurance measurements, and to allow a paper trail of the

equipment performance?

If you look at some of the failures in other equipment that even before this committee -- failures of power supplies, cables, connectors, and so forth, particularly in the buses on the IBM devices can introduce serious problems.

I run a video image analysis lab which started out as a research project, and which is now a service thing for a number of researchers. Although this does not involve humans, we have seen some serious problems with computers that are used over a period of time. Now possibly you junk the equipment after two years and put something else in, but you've got to know when to junk it. I think you need this type of stuff. I would presume that the FDA and its engineering section would be sure that this is included.

DR. HALBERG: Can I paraphrase that as that we need enhanced quality of verification of quality assurance?

DR. GRIEM: That's correct, with a paper trail as to what's going on.

MR. WYSHOGROD: Let me try to cover the points that I understood. First of all, the machine includes a self-test. Upon power up, and even during the measurement, before every reading in fact, that it does an individual

self-test. If there is any failure, it reports, and it reports the source.

Second, the daily verification that you mentioned is what we discussed before. It is the daily verification on the supplied phantom. That is the only device that we supply that in effect checks the entire system from its front, and all the way out to the back end. If there is something that is wrong that fails specification, the result of that is a fail.

You asked about our paper trail and a log. The log includes the 500 most recent measurements. At about 20 or so measurements per month, there are both five months and over a year's worth of back data saved at all times in the system available visually every time you look at the phantom result, and also on the spreadsheet output that we mentioned before.

So the combination insures that you will not make a measurement if the device is not within specification, and you have the paper trail to prove it going back over a year's worth of measurement time.

DR. HALBERG: Does that address your concerns?

MR. WYSHOGROD: I'll comment also that the patient labeling includes this, and specifies a daily verification

check in the morning before you do anything with the system. The whole test takes about one minute total to do.

DR. SMATHERS: Before you sit down, one question. Is the software written such that you must make that test, or the system will not work that day?

MR. WYSHOGROD: No, the software is not written -- you may execute a measurement without that, but we have stressed to every single person, every single customer that has ever bought this machine, that they do this daily verification. We could force them to do it. We don't think it is necessary.

Some people choose not to do a daily verification, even though we think that they should. Some people do a weekly verification. It is their choice. It is more standard and similar to most of the devices that are on the market where someone can choose to do it if they want to. We recommend both in writing and verbally in our training to do the daily test. We think it is important.

DR. HALBERG: Dr. Griem, did you wish to go back to making a motion?

DR. GRIEM: Yes, well, I think I will paraphrase some of the things that Dr. Melton also said. I propose that we vote for a motion for approval with the conditions

stated in the discussion as displayed on the advised first overview that was put up.

And that as Dr. Melton stated, the SoundScan 2000 is a safe device and provides data about skeletal status which is similar to that obtained currently from approved technologies to assess bone mineral density. He goes on to say since there is little or no risk to patients from the device, and there is a potential benefit that patients may derive from this skeletal assessment, the use of the SoundScan is justified.

I move for approval with the changes as indicated.

DR. HALBERG: Is there a second for that motion?

DR. ROMILLY-HARPER: Second.

DR. HALBERG: Let me just briefly restate the motion. The motion is for conditional approval, with the conditions being revised labeling indications and some of the other qualifications we have discussed in terms of the indications for use labeling.

Do we wish to add the other condition that I heard mentioned, which was data on non-Caucasian populations?

DR. GRIEM: Yes.

DR. HALBERG: Let me have a show of hands for those in favor of --

MR. MONAHAN: Excuse me, before we proceed, I would like to clarify the issue of the non-Caucasian population. Are you suggesting that the company strive to get a non-Caucasian reference population, or do a study on non-Caucasians? I'm unclear as to exactly what you are requesting on that issue.

DR. HALBERG: My interpretation was a reference population of non-Caucasians.

DR. HACKNEY: Are we saying they need to do that before they can market this? That's where I'm unclear?

DR. HALBERG: Dr. Alazraki?

DR. ALAZRAKI: No, I think that would be unreasonable. I think the Caucasian population is a high risk population relative to say the black population. The Mexican American population is probably fairly similar to the Caucasian population in terms of risk. I'm not absolutely sure. Certainly they should do that, but that should not be a prerequisite I don't think.

DR. SACKS: Let me just point out one thing, and please, anybody who has expertise in this area correct me if I'm wrong. I don't think that it is the reference population that we want to change in any way. My understanding is that an African American woman and a

Hispanic woman, an Asian woman, and a Caucasian woman who have a T score for example with DXA of -2.5 have the same risk, all other things being equal, of fracturing.

It's just that we do know that different populations may have higher young normal rates, but you would not want to compare to a moving target in that sense. The thing that I think we don't have the data to tell yet is whether or not -- well, let me back up.

We do know that all different ethnic groups tend to decline along the same slope with BMD, that is DXA measurements. We don't yet know for sure whether that is the case with cortical ultrasound until we do long-term studies on that. The reference population I would think still we would want as a stable target.

DR. HALBERG: Do we still wish to include that as an absolute condition for approval, or we would like to suggest to the company that they collect more data?

DR. ALAZRAKI: I strongly recommend that we don't say that's a condition of approval, but that we recommend that it be done.

DR. HALBERG: Okay.

DR. ROMILLY-HARPER: I just think it should be in the definition somewhere that that is the population that

was studied.

DR. HALBERG: Right, I think we inserted the word "Caucasian."

DR. ROMILLY-HARPER: As long as we insert the word "Caucasian," then the market will fall where it lies.

DR. HALBERG: So the condition for approval is really the revised labeling?

DR. ROMILLY-HARPER: Yes.

MR. MONAHAN: For the record, I would like to restate the tentative new indication for use as reconstructed by the panel. The SoundScan 2000 measures the velocity of ultrasound, that is, speed of sound, SOS, in the tibia. SOS through the tibia provides an index of bone strength, with strong bone having higher velocities.

When compared to the results of a reference population of normal Caucasian individuals, the SoundScan measurement provides a risk factor for skeletal fragility. The SoundScan measurement provides information which, when combined with the patient profile and other relevant risk factors may be useful in the initial evaluation of osteoporosis, and as an indicator of future fracture risk.

DR. HALBERG: Everybody okay with that? Can I have a show of hands for the numbers in favor of the motion

which is for approval with conditions? Thank you.

[Whereupon the motion is approved with conditions.]

The recommendation of the panel is for approval with conditions. Can I just have everybody go around and state why they voted the way they did.

DR. HACKNEY: Well, I think as was the case with another one we approved earlier, this gives another method for assessing the strength of the bone we assume, and it will be easier to do and more widely available than the techniques that are currently available. It should be useful.

DR. DESTOUET: The device seems useful, and I think safe and useful in the evaluation of osteoporosis.

DR. ROMILLY-HARPER: I think the device seems like a safe device, utilizing a non-ionizing radiation approach, and can be widely applicable to large numbers of individuals, because there is not a great need for extensive training.

DR. GRIEM: Well, I think the SoundScan 2000 is a device to directly evaluate bone density of the tibial cortex, and maybe a screening tool for the rapid evaluation of clinical problems related to bone quality. The SoundScan

2000 is one of the measures of quantitative ultrasound discussed in the recent review articles, and comes out as a recommendation from these two review articles.

DR. GATSONIS: Although I think this is a safe device and it would be easy to use and so on, in my estimation the methodologic aspects of the proposal did not support the claims about the efficacy of the device. Although this is a kind of device that can be used broadly and easily, it does carry a certain risk in the sense that if the findings from that device are not reliable and not really predictive of the kinds of outcomes that we are saying, they may be generating a lot more exams, a lot more anxiety, and a lot more medical care down the line.

So in that sense, I have abstained. I did not vote against it, but I cannot support this, the indications that are being proposed.

DR. ALAZRAKI: I think that in general in practice of medicine these days we are looking for the more non-invasive, the less expensive, maintaining accuracy always in diagnostic testing. Certainly this falls into that category. Other prototypes have already been through this process, and this is another one down the line. I think that it is going to prove to be a valuable adjunct to the

armamentarium that we have in diagnostic medicine.

DR. SMATHERS: I would concur with many of the other comments. I would have to say though that the whole are of bone mineral density suffers from statistical insignificance. This is no worse than other devices that are currently approved and being used.

I tend to hope that the physicians will not hang their hat on a number that comes out of a single device like this, where we saw three patients presented, none of which were statistically significant. The normal and the supposed disease patient overlap quite readily, but given additional medical information and diagnostic information, it may be as was stated, a piece of the puzzle. To that extent it will do no harm. I'm not sure how much good it will do.

DR. KOPANS: I was actually going to abstain had that been an option. I think Dr. Gatsonis has outlined my concerns. I guess I come from a background where screening tests require prospective randomized control trials. I understand the problems in doing that and the great cost.

The reason I was going to abstain as opposed to voting against it was that my understanding from this meeting is that there are other devices that have been approved with similar levels of evidence, although I am

surprised at that.

DR. HALBERG: Thank you. Any other comments? If not, I think we will break for lunch, and we'll make it a short lunch so that we are all back at 12:30 p.m. to start the afternoon.

[Whereupon the meeting was recessed for lunch at 12:02 p.m., to reconvene at 12:30 p.m.]

A F T E R N O O N S E S S I O N [12:37 p.m.]

DR. HALBERG: We will now proceed to discuss with consideration the second PMA to be discussed today.

Good afternoon.

Agenda Item: TransScan Presentation of P970033

We will begin with the presenters from TransScan and they will be talking about PMA Application P970033 for their T-Scan 2000 intended to use, impedance to help distinguish between benign and malignant lesions in women whose mammogram is indeterminate.

I request that the presenters for TransScan, the sponsor of this premarket approval application, sit at the presenters' table. I guess most of you are already there. And after you have all finished with your presentations, I would also ask that you turn the presenters' table over to the FDA speakers, who will follow you.

It looks like Mr. Neugebauer is already at the microphone. He is president of development for TransScan, who will begin the company's presentation of the information contained in the PMA that we are considering today.

Mr. Neugebauer.

MR. NEUGEBAUER: Yes. Good afternoon, ladies and gentlemen. My name is John Neugebauer and I am the U.S.

representative for TransScan Research and Development of Miguel Halimic(?) Israel and its wholly-owned subsidiary, TransScan Medical of Ramsey, New Jersey.

We are a privately-held firm established in the State of Israel in 1993 with a mission to develop and bring to market a remarkable new technology in the field of breast cancer detection. To that end we are very excited and honored to share with you today the results of our labors and, perhaps, more importantly, the significant results of our clinical studies.

On behalf of all TransScan employees and associates in both Israel and the United States, we sincerely thank the panel for its time, its resource and particularly its attention in reviewing our PMA today. We, of course, have a great deal to cover in a very short period of time.

I am going to ask that if you have questions, if you will try if at all possible to hold them until the end of the presentation. I would like to begin with our first presenter and introduce Dr. Andrew Pearlman. Dr. Pearlman is our vice president of technology and our chief scientist.

He is a Ph.D. in biophysics from the University of California and he is the founder of TransScan Research and

Development.

Dr. Pearlman, please.

DR. PEARLMAN: Good afternoon, ladies and gentlemen. I would like to echo the thanks offered by John Neugebauer to this panel and to the assembled people to offer us the opportunity to share with you something which we believe is truly exciting and which we hope to convince you by the end of the discussions is safe and effective for use as an adjunct to mammography in detection of breast cancer.

I would like to just take a moment to express my feeling of gratitude that we have been able to reach this moment because this is, in a sense, a historic one. This is the first time that we are aware of that a commercial device involving the technology of electrical impedance imaging has been brought to the FDA and, indeed, to the public at large.

This is the culmination of decades of scientific research into this field, as I will quickly review, and involves the detection of phenomena that are significantly different or in a different modality from those that are used today and, therefore, offers information that can help in an adjunctive way.

First of all, why do we need an improved adjunct

for mammography. Mammography is the gold standard, as we know, but as we also know from various reports, the rate of negative biopsies in the United States ranges from 75 to 80 percent, sometimes even higher. This involves a very high cost and trauma to patients and, nonetheless, we still have false negative rates, meaning missed cancers, in anywhere from 15 to 25 percent, depending upon the age group and, in particular, in the patients under 50 years.

Further, a significant percentage of the findings are equivocal, i.e., are not clear in their implication and could benefit from additional information to try to result in patient management.

In addition, mammography involves radiation risks, which limit frequent follow-up and other adjuncts, which exist, such as ultrasound, MRI and others, have a high cost. So, for all of these reasons, there is the potential need and desire for an additional adjunct that can answer some of these problems.

We are speaking about breast impedance imaging. This involves the formation of a map or image of the electrical impedance of the breast. This is derived in real time and involves the direct detection of neoplastic tissue by virtue of the different properties of that tissue in its

electrical conductance and capacitance compared to the surrounding tissue.

This device involves no radiation. It involves no risk or discomfort to the patient, as we will demonstrate from our study. It is a rapid exam. It is low in cost and it provides results on the spot.

All of this is based on decades of work that has been done in investigating the impedance characteristics of malignant versus normal tissue. These studies all indicate that when you have malignant tissue, the changes at the cellular and histological level cause changes in the capacitance and conductivity properties vis-a-vis the surrounding normal tissue.

These are owing to such factors as changes in the membrane, involving the breaking up of tight conjunctions between adjacent cells, modification of membrane proteins. This leads to increased permeability of ions through the membrane into the cell and out. All of this causes ultrate(?) cellular water content leading to intracellular and extracellular fluid ratio changes.

Also, the cells tend to have a different packing density and orientation. All of these properties affect the local impedance properties of the tissue compared to the

normal surroundings.

Now, before we proceed, I need to have the mobile microphone.

As I mentioned, this has been known for some time and what we are seeing here is an example from a 1988 article in which the authors had taken immediately mastectomized breasts, had taken sections from those breasts and you can see here, this is a section through the mastectomized breast. The dashed area indicates the tumor. They took cylindrical samples in the tumor area adjacent to the area and distal from the area and measured in an impedance analyzer the conductivity and dielectric constant properties of the sample tissue.

What do we see? That the normal tissue represented here by the Vs taken from far away has a relatively low conductivity and here you can see also the dielectric constant, which is related to the capacitance is also quite low. And by contrast in those same samples -- I am sorry -- in the samples taken in the tumor area, we have an elevated conductivity and an elevated dielectric constant.

These differences, as you can see, are on a logarithmic plot. You are not talking about a few percent.

You are talking about order of magnitude or more. So, these represent a potential, powerful marker at the cellular level, characteristic of malignant tissue. And this is the basis on which this is based.

As mentioned, this is based on many, many projects done over tens of years. These are simply -- they fall into groups of in vitro studies, in vivo studies involving invasive measurements and in vivo studies involving non-invasive. Just to give you an idea, this has been around for some time.

What is new? The T-Scan implements a non-invasive way to detect these impedance differences on a local basis. How do we do that? Well, if this represents a tumor located underneath the skin at some depth, it has a lower impedance than the surrounding tissue so that if we apply a small electrical signal, typically in the range of one volt and varying frequency range to the hand and then apply an array of sensors at the breast.

The current goes from the hand. By the time it gets to the breast, the current field is reasonably homogeneous and is disrupted by the presence of this impedance object, causing a change in the current density, which we detect at the surface. This is the basis of the

detection method.

This represents the T-Scan recorded, using that probe that we just showed in the diagram. This is one sector recorded by that probe shown here. We record nine around the breast, including right on the nipple. The patient is typically supine during recording. This is the capacitance where the bright -- that is, the gray scale is proportional to increasing capacitance. You can see the nipple is bright right and left. This is the patient's left and right breast.

This is the same right and left breast viewed and conductivity. This is a typical normal patient's exam. By contrast, I think you can see that we have something interesting going on here. This is an invasive carcinoma, about 8 millimeters detected in this patient, same display, same format.

At this point, I would like to just show you how this exam is done and just briefly show you what the T-Scan if you will look at the video monitor over on the right. I am going to narrate this briefly as we go.

First, a brief review of the device. This is the display monitor. We control it by typical key and mouse. It has the ability to store data on a removable disk or

floppy and hard copy is performed on a typical laser printer.

This is a typical display, such as what we just showed. This is the scan probe, which has built-in controls that enable to control all the necessary functions for the examination, while holding the probe so you do not have to distract yourself from the examination itself. As we will point out, it is important to hold the probe correctly, to position it correctly and so forth, so that we didn't want to have distraction of the user from that.

These are the sensors on the bottom side of the probe that contact the skin intimately to obtain electrical current measurement. This is a model that we will see demonstrating the technique. An electrode is attached to the arm or metal cylinder held in the hand. The patient lines supine. We elevate the same side so as to present the breast vertically. We make note of any skin marks that appear on the patient's breast because some of these can cause artifacts.

We apply a conductive fluid. This is a commercially available conductive fluid to improve contact and we put typical conductive gel, such as used in ultrasound or an EKG, on the probe to complete the contact

and avoid air bubbles.

The examiner is now recording the nipple of the patient. I believe we will see -- there is the nipple in real time. That dark spot you saw popping into the white, that is a bubble and this is part of the examination technique to know how to remove the bubbles. Then we proceed in a counterclockwise fashion to record the upper, outer right breast sector. Then we proceed -- as you can see there is a sort of a scooping motion from outside the breast towards the middle to minimize the breast mass underneath the probe as we record going counterclockwise, a total of nine sectors to cover the entire breast.

We also have another view. We call this our anatomic screen, where we can record high resolution views at any position without sticking to the 3 by 3 format. That is basically it.

If I may, I will just proceed from here if that is all right with you.

This device was built on the experience of a prior technology that was developed at the Whitesman(?) Institute in Israel. This was called the MammoScan. The MammoScan was developed at the Whitesman Institute and then tested in Italy, in Pestori(?), Italy, by Dr. Jan Carlo Peparno(?).

Since the 1980s, he recorded more than 6,000 patients reported in the first paper published on this in 1990. In that study, they had 745 biopsies that showed a good correlation between the MammoScan indications and the pathology.

This demonstrated both the safety and the fundamental feasibility of this technique and basically convinced us that we should go ahead and develop a commercial version of this device updated for the 1990s. There have been since 1982 more than 16,000 examinations repeated with this device in the site in Italy and now many sites, of course, outside the United States that have the T-Scan, plus the study centers in the United States have completed many thousands of more examinations, establishing the safety of this device.

In 1996, upon development of the new T-Scan 2000 system, we conducted a pilot study in Israel; 470 patients involving 293 biopsies. You can see 49 malignancies, 244 benign. The overall sensitivity of this was about 80 percent with 74 percent specificity.

I want to point out that this was performed in a typical clinical mode, i.e., the doctor knew that there was a mammographic finding that they wanted to investigate and

put the probe where they thought there was concern and then judge whether it was positive or negative.

This led to the approval by the Israel Ministry of Health of the device about a year ago and led to the study that we are presenting to you today. This study is aimed to test the hypothesis that the use of T-Scan 2000 has an adjunct to mammography results in higher diagnostic accuracy for breast cancer than the use of mammography alone.

As has been pointed out in previous studies, such a study requires rigorous scientific design and avoidance of bias. Therefore, in the study design we incorporated blinded recording. This means that the examiners who are technicians knew nothing about the patient's status, nothing about the mammographic findings, nothing about palpable masses. They simply recorded the images in the standard screening mode, if you will.

Then when they were read, they were read blindly; that is, by people who were not involved in those patients at all and knew nothing about them, knowing only the image and the age of the patient. The study was multi-center, conducted internationally in the United States, France and Israel and involved the comparison of the T-Scan image by itself, the mammogram image by itself and adjunctive

readings against biopsy results.

Now, when I say mammogram by itself, we are referring to the standard screening mammograms most recently recorded and we reemphasize that so there would be a standard set from all sites, from all patients in the same, so that we could have a standard against which to measure and the T-Scan exam was a standardized T-Scan exam without targeting, without knowledge and without high resolution close-ups, so that we could have a standardized T-Scan exam to compare. So, both were standardized.

This was a strict scientific protocol, which varies from the recommended use mode that we will discuss later.

Inclusion in the study involved two groups of women, biopsy cases. These are patients that had one or more suspicious lesions discovered within 12 weeks of the T-Scan exam, either by mammography or palpation or by ultrasound and the patient was scheduled for open or core biopsy for that lesion.

Screening cases involved patients who had a routine screening mammogram within 12 weeks of the T-Scan examination. Exclusion criteria, the primary ones were that if a patient did not have a mammogram within the specified

12 weeks, we excluded pregnant women and women with electrically-powered implant devices, not because we know of any actual risk but because all of the experience in Italy was collected this way and we didn't want to defer from that in this study.

We did not record patients who had only one breast nor did we record patients with breast implants. We tried to keep it straight and simple. We similarly excluded patients who had had a recent surgery or a thoracotomy, that is, within three months prior to the exam. If the needle biopsy had been performed very recently, it often causes an artifact so we have at least two weeks before any previous needle biopsy.

If they were undergoing chemotherapy or radiation therapy, they were not a candidate for this study. If they had incomplete or technically faulty T-Scan data, based on objective criteria, that is, missing data, missing sectors or only one breast recorded, they were not includable or if they had a physical abnormality that prevented reliable placement of our probe. We had very few cases of that.

The patient information required in order to enter into our analysis was a completely -- corrected, completed T-Scan examination recorded in the memory, original

mammograms and I underline "original mammograms," preferably a full four view set, the mammography report and the pathology report for biopsy cases.

When we gathered all these cases and examined who is fully ready for re-reading, a case was excluded only if there were original mammograms not available, which did occur in quite a few cases or if the original mammograms were out of date; that is, more than 12 weeks away from the T-Scan exam or if they had an incomplete T-Scan data, meaning that the image was not recorded completely. There were missing sectors or a whole breast.

We used the services of an independent statistical center for the study, which was at the University of Cincinnati Medical Center. Professor Ralph Buncher is going to follow me shortly to present the results of the study. Prior to sending the data there, there were three different levels of data; quality assurance at the site by the site data manager. The application specialist from TransScan was operating as monitor in each country to make sure that the protocol was being complied with.

And we had the clinical administrator of TransScan overall responsibility for checking all of that and then they were also checked by the Statistical Center. Just one

more time, it is an important point, why did we have a blinded recording and re-reading rationale? This is so that we could, first of all, test the hypothesis that T-Scan detects cancer better than chance.

Of course, if you record the T-Scan targeted by other information, then you don't know who is helping who more. So, you need to have a blinded recording to address that key question.

Secondly, we had to have a standardized exam, as I have just mention, both the T-Scan and the mammogram, to enable head-to-head comparison and then if you, of course, use the adjunctive examination, then you could have diagnostic mammograms that sometimes have previous mammograms, sometimes have compression views, sometimes don't. Sometimes there was ultrasound and sometimes don't. So, you would have an unstandard set from each patient and that was not viewed as a good basis for analysis.

To eliminate bias, as I mentioned, the examiners were blinded to the other information. The readers were blinded to all patient information, except age, and they were also blinded to the composition of panels. "Panel" refers to the set of 40 to 60 cases that we had in one reading sitting, gathered typically from one center and read

by the reader from another center.

These comprised cases that were made up of biopsy positive, biopsy negative and screening cases and that is the other point I want to point out is that we did include approximately 30 percent of the cases were screening patients and this was done to avoid the bias that the re-readers would be able to say we know that somebody sent this patient to biopsy because they don't.

This was very important. I won't go through all the steps in exam but there was a standard examination procedure that was followed and that was part of the training at the sites. I just will briefly mention that there are artifacts. It was mentioned in the film. External lesions, such as moles and scars, can cause on occasion, very often actually, a bright spot that you have to identify, which you can do while you are examining the patient. It is quite easy to do.

There are some normal anatomic variance, such as the nipples, which tend to be bright; informammary(?) ridge, which sometimes shows a long, horizontal brightness. Costracontrajunctions(?) when inflamed to be bright and ribs sometimes gives spots. And all of these are identifiable by procedures that we train the technicians, when they are

learning to do this to rule them out.

If you have poor contact between the probe and the skin, you can get contact artifacts and that includes bubbles, all of which with proper training are avoidable.

The T-Scan has a very simple reading criteria in that sense. There are only two criteria that we looked at in the study. One was very substantial nipple left/right asymmetry, meaning that one nipple was substantially brighter or larger than the other. And the other were isolated focal brightness, incapacitance, conductance and two parameters that were derived from the impedance spectrum that we measured called P1 and P2, relating to phase.

These parameters were those that displayed to the reader. I won't go into a lot of depth, but there was an algorithm developed before we commenced the readings that involve the -- the reader enters basically whether they see a spot or not. That will be discussed in a moment by the next speaker.

Then there was an algorithm, which converted that into an LOS or level of suspicion scale of 1 to 5 and this is simply how it did it. We can follow this up later if you are interested, in more detail.

At this point, I would like to introduce the next

speaker if I could, Dr. Michele Rossmann from the Sinai Women's Health Center in Detroit. She is the director of breast imaging. She was a reader in our study and a PI at her site.

DR. ROSSMANN: Good afternoon. My name is Dr. Rossmann and I am from Detroit Medical Center, Sinai Women's Health Center and Wayne State University.

I would like to explain to you this afternoon just how we did the readings for the panels. We were given the images and the ages of the patients only. No other information was provided to us. The set of T-Scan images were read and scored first. Each panel contained 40 to 60 cases. This took two to two and a half hours.

Then for each mammogram in the set, the mammogram was scored alone. Then the mammogram and the T-Scan were read adjunctively per the adjunctive scoring procedure, which I will explain next.

In reading the T-Scan, the reader reviews the image for each of the four impedance parameters, CAP(?), CON(?), P1 and P2. You rule out any normal variance and artifacts and then you note the findings. First, is there asymmetry of the nipples? Second, you look for bright spots. If it is an isolated bright spot, it is considered

positive and given a 2.

It is given a 1 if it is equivocal, probably representing a normal variant or artifact and a zero if there is no spot. The computer calculated a breast score of 1 to 5. Now, in scoring the mammograms, the reader was instructed to assign a score of 1 to 5 to each breast and to note the location of the finding as on the hour of a clock.

These are the different levels of suspicion and I will explain them further. Level of suspicion 1 was negative. It corresponded to 0 percent probability of malignancy or to both of the ACR BI-RADS 1 and 2 scores. Level of suspicion was benign. It was assigned by the reader of almost certain of a benign finding; that is, a very low probability of malignancy approximately equivalent to the ACR 3 score or the 0 to 2 percent malignancy range.

Level of suspicion 3 was probably benign. It was equivalent to the lower portion of the ACR 4; that is, the portion with the probability of malignancy from 2 percent to approximately 50 percent. Level of suspicion 4 was probably malignant. It corresponded to the portion of the ACR 4 with the probability from 50 percent to the division between ACR 4 and ACR 5 on the probability access.

Level of suspicion 5 was highly suggestive of

malignancy. It was equivalent to the ACR 5 score and although not formally defined, it was typically in the range of 75 to a hundred percent.

Now, the adjunctive reading and scoring. The first step is to review the mammogram in the vicinity of the T-Scan finding and update the mammographic score if there is a new focal finding. If the mammogram has no focal finding, the adjunctive score equals the mammogram score and the adjunctive score is complete.

If the mammogram has a focal finding, you proceed to step 2. In step 2 we look at the T-Scan. If there is nipple asymmetry, then either side is considered abnormal and would be a match with the mammogram finding. If there is mammographic abnormality in a corner of the breast in one of the outer quadrants, then if there was a T-Scan abnormality in any of the 1, 2, 4 or 5 boxes, then that would be considered a match.

If there was a mammogram abnormality on the side of the breast, either medial or lateral, if there was a T-Scan abnormality either on that side or in the middle row, then that would be considered a match. If the mammogram abnormality was in the middle of the breast, that is, behind the nipple, then any of the different sectors of the T-Scan

would be considered a match.

The score, the adjunctive score, was increased by one if the T-Scan has one or more spots in the vicinity or nipple asymmetry; that is, the adjunctive score would equal the mammogram score plus one, with a maximum of 5. The score was decreased if the T-Scan had no spots in the vicinity and no nipple asymmetry. The adjunctive score equaled the mammogram score minus 1 with a minimum of 1.

The score was unchanged if the T-Scan is equivocal in the vicinity. Then the adjunctive score equals the mammogram score.

Finally, a positive was considered an LOS of more than 2 and the patient would be managed with biopsy. A negative was considered an LOS of 1 or 2 and the patient would be managed with routine or short term follow-up.

Now I would like to show you a few cases. These are bilateral oblique(?) views from a mammogram. This patient had a palpable mass in the right retro areola region, which would be generally this area. There really is no focal mass there, maybe a suggestion of a nodule or abnormality here. But, of course, a mass might be obscured by the surrounding dense tissue.

On cranial caudal, there is no suggestion of a

focal mammographic abnormality. This patient had a T-Scan and there is a very hot spot at the 12 o'clock position in the same breast, which corresponded to the palpable mass. The palpable was excised and represented an infiltrating ductile carcinoma.

The second case, there is a nodular abnormality, a nodular density in this region on the medial lateral oblique, which is actually lateral in the left breast on T-Scan. No focal abnormalities were noted. Therefore, there was a negative T-Scan. This abnormality was core biopsied and represented a benign introductile papilloma.

The third case, there is a nodular density in the outer aspect of the --

DR. KOPANS: Can I just interrupt? Can you just go back to the last T-Scan? What do you do with the bright spots that are on the T-Scan there? I know you didn't want to be interrupted. I apologize for that, but the bright areas in the --

DR. ROSSMANN: These are rib artifacts and when you are trained to use them, when they occur during the edge and they are kind of fuzzy looking and this would be a perfect place for rib artifacts. Also, when they are very linear looking like this, it tends to be rib artifacts.

DR. KOPANS: What if the lesion were out laterally near the ribs, how would you --

DR. ROSSMANN: Usually it is more focal and bright, sort of like the one I showed you in the first case. In this case there is a nodular abnormality in the lateral aspect of the left breast. Actually, it is upper outer quadrant. It is best seen on the medial lateral oblique. The T-Scan, again, was negative.

Again, these are some rib artifacts. They are very common in the outer aspect in the peripheral quadrants. You also have to realize that we are reading both CAP and CON and P1 and P2 and we are not showing you P1 and P2, though they all look like the bottom.

DR. SMATHERS: Can I ask a question? The nipple differences appear to be substantial here and, yet, you are not reading that as a difference.

DR. ROSSMANN: We have a special screen that we read for nipple abnormalities and that is actually the first thing you do in the exam. It is actually button No. 1 above there. And then you get a very nice, clear picture of the nipples and that is how we read the nipple asymmetry.

Anyway, this was core biopsied and represented a fiber adenoma. The last --

DR. KOPANS: How was that last one graded based on the mammogram, do you know?

DR. ROSSMANN: I am sorry?

DR. KOPANS: How was the last one graded based on the mammogram, LOS?

DR. ROSSMANN: On the LOS? I think it depended on who rated it.

DR. PEARLMAN: I believe it was a 3.

DR. ROSSMANN: I think it was a 3. And went down to a 2. That is right.

The reason the patient went to core biopsy is the patients were managed with a -- by the center clinically and then they were read afterwards in a blinded fashion. So, it didn't interfere with the care of the patient. It didn't change the care of the patients.

This is the last case. There is a nodular density in the medial aspect of the left breast, probably in this area. The T-Scan was negative. This is, again, a perfect example of rib artifact along the edge like this and contact artifact here. You often times get that by the nipple, where the areola meets the regular breast tissue, breast and skin.

So, this was considered a negative T-Scan and this

went to core biopsy and was fibrous cystic changes.

DR. PEARLMAN: Can I just emphasize this? It was negative on the left breast in particular.

DR. ROSSMANN: Yes.

Thank you.

DR. PEARLMAN: Thank you, Dr. Rossmann.

Now, understanding how these were read, what were the results that we obtained, we would like to invite our next speaker, Professor Ralph Buncher of the Department of Biostatistics and Epidemiology from the University of Cincinnati Medical Center.

Professor Buncher was the statistical director of this study. And as I mentioned, the University of Cincinnati Medical Center was our independent statistical center for the study.

Professor Buncher.

DR. BUNCHER: Good afternoon. I am missing my class, so this is the best I could do.

These are the results that we had in the study that you have read about, but I will take you through.

There were a total of 2,456 enrollees. Of these, 882 were in the biopsy category and of those, the criteria that Dr. Pearlman talked to you about were met by 481

individuals. Those 481 individuals produced biopsy readings on 504 breasts. There are 23 that are in there with both breasts.

The other side, the screening group, 1,094 met those criteria and of those, a group of 264 were selected to be contemporaneous with the other patients and that supplied 528 breasts that were used in the study.

We have talked about the panels. These are the panels. There were the U.S.A. panels, the French and the Israeli panels. Each panel consisted of biopsy cases that are positive and negative, plus screening cases to supplement and to provide more negative findings so that the readers did not know what was to be there.

There were a total of 359 individuals and from the U.S., 386, from other countries and a total of 745 persons, women, and, therefore a total of 1,490 breasts that were studied. The age distribution covered a wide range with about 45 percent of the women below the age of 50 and the other 55 percent of the women above 50. We attempted to get all ages that were appropriate.

The tumor size distribution, again, some 45 percent of the cases were a centimeter or less. The other 55 percent were larger than 1 centimeter. About 45 percent

of the women had a palpable mass and the other 55 percent did not.

Some 45 percent were premenopausal and 55 percent, approximately, postmenopausal and about 20 percent of the women were on estrogens with the others not on estrogens.

Now, when we get to the results, these are the mammogram results for the people who were actually positive in biopsy. You see the readings of the level of suspicion scale. You see then when T-Scan was used in the adjunctive mode, the change in the distribution in these positive cases, there is a decided movement towards the more positive. Most of the change, of course, is this plus 1. So, many of these 4s become 5s.

The key that we are discussing this afternoon is primarily the indeterminate cases. Those are those that are designated in the LOS 2 and 3 category. It is these cases originally. And if you look at the ratio of 3 to 2s, you can see that for these positive cases, the ratio of 3 to 2s has clearly gone up, thereby indicating that more of the positive cases are picked up by the T-Scan in the adjunctive mode in combination with the mammography.

When one gets to the negative cases, the complementary picture is found. Here is the distribution of

the mammographic reads, a sizeable number of 3s in these cases that were found to be negative, a shift in the distribution, moving them to the less positive side and, again, the 3 versus 2 in the readings in the adjunctive mode, there is considerably more 2s than 3s; whereas, in the reading in mammographic alone, there are considerably more 3s than 2s, again, indicating a movement towards the more accurate reading.

The results that you have seen in your materials, there are 504 breasts total; 179 positive, 325 negative, and we get the typical screening results of sensitivity and specificity. The sensitivity goes up a little bit. The specificity goes up to a considerable extent in this whole body of data and the -- we will show you some P values afterwards.

The U.S. cases alone reflect essentially the same picture. The numbers of sensitivity and specificity are comparable in the U.S. cases, as in the total group; therefore, implying that both the U.S. and the non-U.S. have essentially the same results.

Statistically what we are looking at here is the question of the off-diagonal terms, the terms in which the two groups disagree. If they are both positive or they are

both negative, they don't provide us with any information about which one is better and it is the better question we are asking here.

As a way of putting this more simply, the positive cases are a win for the adjunctive read if they are up here in this cell, i.e., found to be positive by adjunctive negative by mammogram and a loss in the comparable off-diagonal turn. In the biopsy negative cases, it is the other way around and these are wins for adjunctive and losses. And, so, we are presenting the results in terms of wins and losses. It just seemed simpler than to try to keep track of which is positive and which is negative at any given moment.

Win is good for adjunctive read. Loss is bad for adjunctive read.

When we put out the total record of the five levels, the key boundary is where the strong line is drawn. So, all of these cases -- and these are the positive cases -- all of these were positive in both modalities. These were negative by both modalities. So, it is the off-diagonal terms that are of interest.

We see a total of 16 cases that are, quote, wins for the adjunctive mode and eight losses. If one restricts

the attention to just the interdeterminate to 2s and 3s, then the numbers become 15 and 8.

The eight cases are detailed for you in the materials you have and in several of those cases it was an error in that the rules were not followed. The vision was correct. The observation was correct, but then when the material was recorded, it was not recorded correctly and that is what led to about three or four of those errors.

The negative cases, again, we turn ourselves around, these are all -- these are the ones that are incorrect -- let's just say it this way -- the off-diagonal terms are here and it is the 69 cases that are wins for the adjunctive read. There are these 32 that are losses for the adjunctive read. So that when we look at the total of these 132 cases, there is a net loss of or a net reduction of unnecessary biopsies of 28 percent. All these women were sent to biopsy.

So, if the adjunctive read had been mode, then 28 percent fewer women would have gone on to biopsy. They could have been followed and not biopsied.

It is, of course, important that no individual is contributing too much to this sets of differences and, so, we have given you a letter that indicates the readers here

-- and there are a couple of readers that are in there twice and one that is three times and what we find is in terms of the wins, there tends to be a spread of those wins and not any single person that dominates that field.

In the negative cases, again, we see that virtually every individual that is reading has an improved set of read on those cases and, in fact, with each of those people would send more people to be followed up and fewer to biopsy had the adjunctive means been used.

This last reader down here, the anonymous Dr. J, you will note, did a particularly poor job and this reader managed to get very bad results compared to everybody else. Some would contend that this person would be an outlier, statistical outlier, and throw that person out of the consideration. Had one done that, this 21 and 16, subtracting these numbers, becomes 18 and 2, i.e., that would be a tremendous win for the adjunctive.

I am a purist. So, we didn't do any such things and we also left all eight of the cases in on the positive side that would have gone the other way, three or four which were explained. But, again, let's leave all the cases in and do the analysis with all the materials regardless of why or wherefore.

This takes us down to the indeterminate cases, the indeterminate cases being the LOS 2s and 3s. And you can see that there is a clear statistical advantage in both the -- in the specificity for all of the LOS cases, whether it is all of the cases or just restricted to the U.S. data.

When we subdivide by various factors, you see that, again, we can look at the under 50 and the over 50. There appears to be a mistake that was in your book. And you will see two things. One, the specificity is statistically significant in both the younger than 50 and the over 50.

And, interestingly, that in the under 50, the sensitivity is statistically significantly improved. That observation is then found when we look at premenopausal and postmenopausal, where, again, there is a statistically significant finding of sensitivity in the premenopausal women. So, one believes that for the younger women, the under 50 women, there were two advantages, just both the sensitivity side, as well as the specificity side.

In terms of size, again, we have divided the group into those tumors that are less than 1 centimeter, those that are greater than 2 centimeters and those that are 1 to 2 centimeters. And there is a consistent pattern of

improvement in the specificity. The sample sizes get small on certain numbers of these. So, the statistical significance starts varying at that point.

In terms of the non-palpable and palpable, again, the results are comparable in terms of findings of the adjunctive read for the specificities and sensitivities.

In terms of breast size, again, the results are roughly comparable regardless of breast size in the adjunctive read. You might note that the changes or the differences are larger in the mammographic read. The mammographic read appears to be a little more sensitive to size.

The no estrogen and estrogens, the smaller number of estrogen group, there is statistical significance in the no estrogen group, not in the estrogen group.

Once in my good past, I got involved in the first multi-center study of CT scan against radionuclides and it was a wonderful study because there is a wonderful shift in the ROC curve. We were looking for brain tumors. And there is a decided shift in the whole ROC curve.

When there is a decided shift in the whole ROC, then one says this new modality should replace the old modality. That is exactly what happened in the world of CTs

and radionuclides. We are in this case not in that situation. We are in a situation where all that is being described is an increase in the indeterminate cases, in these cases in the middle of this ROC curve where with -- let's put it this way -- there is a decided improvement in specificity without a loss in sensitivity; in fact, with a slight gain in sensitivity, but, again, a decided increase in the specificity of the cases at that stage.

So, in conclusion, what the statistical analysis seems to show is -- and we didn't show you the data for this, but the T-Scan detects the cancer better than chance. That is a sort of requirement. The adjunctive T-Scan mammography combination then is clearly better than -- has better results than mammography alone and the patients that can benefit are those with an indeterminate LOS 2 and 3 and that such factors as age, menopause and tumor size have not been shown to affect the results.

Thank you.

DR. PEARLMAN: Thank you, Dr. Buncher.

Our next speaker will be Dr. Scott Fields and he is --

DR. HALBERG: I know you had asked us to hold questions until the end. Will anybody be addressing in the

upcoming talks what happened to -- you know, you start out with 882 patients and went to 481 that you used. Will you be sort of discussing how you got those numbers?

DR. BUNCHER: Sure. Let me say that right now. The 881 were the women that had a T-Scan examination. The requirement was that you had to have a mammogram that was within 12 weeks of that T-Scan. In other words, if you were going to surgery from a mammogram that was 13 or 14 weeks old, then you were not eligible.

So, the only women that were dropped out of the study were the women that did not fulfill the requirements of having a complete T-Scan examination, a complete mammogram and have the complete -- and the biopsy, of course, and, so, other than that, every woman that had that combination was there.

DR. HALBERG: Almost half the women fell out.

DR. BUNCHER: Sure, because they didn't have comparable mammograms at that point.

DR. KOPANS: Didn't the protocol require that they have a mammogram simultaneous with the T-Scan or not?

DR. PEARLMAN: Yes, indeed, they did. The problem was that many of these centers had difficulty retrieving the original mammograms and when we finally got to read them

some year later or eight months later, many of the biopsy patients had taken them with them in their follow-up treatment and it was difficult to retrieve them. We made major efforts to do so.

DR. HALBERG: Because there were like 178, I think, that were --

DR. PEARLMAN: No, there were about 380 out of the total. Almost all of them were missing mammograms. That was the reason why they weren't included.

I just want to introduce Dr. Scott Fields, who is director of radiology at the Mt. Scopus(?) campus of the Hadassah Hospital in Jerusalem. Dr. Fields is both a participant in the study and a reader, as well, and a clinical user of the T-Scan in the intended use mode.

And he will be speaking to the use of the machine in the recommended mode of usage, which is what they are now doing at the Hadassah Hospital.

DR. FIELDS: Good afternoon and thank you.

I think I am also supposed to tell you that TransScan is paying me for my time and expenses.

I did participate in the study and since the conclusion of the study in the late spring, I have been using the T-Scan in an adjunctive mode on the indeterminate

patients. I use this in an adjunctive, targeted mode, where I can use the examination optimally. I can position the patient any way that I like. I can position the breast away from any artifact of the skeleton or I can compress the breast in any way I want.

I do an anatomical mode predominantly and I try to come up with an answer on the indeterminate lesion.

I am going to show some slides, just some typical cases, some interesting cases. I don't know if they are going to show, but there are some microcalcifications up in here.

I don't know if they show up in here, but they are in this area of density. There are a few microcalcifications. This was the T-Scan showing an area of increase, capacitance and increased conductance in that area. This was a ductile carcinoma in situ.

This was a case that I brought along just to show that we can have good depth resolution. This was a moderately fatty breast, moderate size breast, with a small lesion close to the chest wall and we are able to see this lesion quite well with increased conductance. This was a ductile -- this was an infiltrating ductile carcinoma.

This case --

DR. KOPANS: Can I just interrupt you quickly on that?

DR. FIELDS: Sure.

DR. KOPANS: On the mammogram, the lesion was in the center of the breast. How did you move the breast so that on the T-Scan it is in the upper outer quadrant?

DR. FIELDS: Well, the breast is quite mobile, especially when we press with this probe. As you saw on the area, we can push -- when you push the breast on this probe, it doesn't exactly correlate. It is more like a regional -- it doesn't send a one-to-one spot correlation.

DR. KOPANS: Have you done any study where you put a needle in under T-Scan and then confirmed it with the mammogram?

DR. FIELDS: No. We don't at the time have a T-Scan needle biopsy device, although that is being worked on.

There are a few microcalcifications right up in here. They are up here in this area. The T-Scan was negative. This was a case of fibrocystic disease.

This woman had a lumpectomy about a year ago, a year prior to her -- to the study. She came back for a follow-up study and she had an area of increased density

with some distortion.

Here it is on the medial lateral oblique. The T-Scan was negative for both breasts. This was on biopsy a post-biopsy scar.

This woman had some fullness in the axillary tail of her right breast. Difficult to depict all that area on the cranial caudal view. The T-Scan was completely negative in that area. We elected to follow-up this patient and she has now come back for her six month follow-up mammogram without any significant change in her mammography.

Just a cranial caudal view and she has not had a biopsy.

What I would like to show now is the flow chart of how I think -- how we use the T-Scan at Hadassah Hospital at Mt. Scopus. We don't examine patients that are equivocally benign or normal. We don't examine patients that I think are almost certainly benign with an extremely low risk of malignancy. We don't examine patients that are probably benign or almost certainly benign.

What we do examine are the indeterminate cases. Those are the ones where I am not sure I should biopsy or I shouldn't biopsy. I am sitting on the fence. I use the T-Scan information to help me decide should we biopsy this

patient or should we not biopsy this patient.

This is the area where the data from the study shows that there is useful clinical information in these patients. You will notice that I don't have LOS scores here. I don't use the LOS score in an adjunctive mode, in the clinical mode. We have to decide each patient individually. We use all the data, as opposed to the study, which we are only given the T-Scan frontal view and the fore view mammograms.

We use all the data we can -- I can use compression views or ultrasounds or whatever I have to help me to get into this -- to help me decide in which category the patient really belongs and I examine these patients where after all the information the -- I am still undecided and I think that the T-Scan provides useful information in this category.

Thank you.

DR. PEARLMAN: Thank you very much, Dr. Fields.

I would like to invite our next speaker, Dr. Thomas Julian, who is the assistant director of the Division of Surgical Oncology at Allegheny General Hospital in Pittsburgh, Pennsylvania, to speak to the implications of all of this for patient management.

Dr. Julian.

DR. JULIAN: Thank you. Good afternoon.

Just a little bit about myself, at the -- we were one of the participating centers and I practice as a surgeon in the large multidisciplinary breast clinic, which participated in this trial for the FDA. My time and travel are being compensated by TransScan for the purpose of this presentation.

As has been presented today and in the PMA, the T-Scan is a safe device. There are no reported complications. As has already been noted, the T-Scan can detect cancer better than chance. The adjunct T-Scan mammography score is better than mammography alone in those groups that have been analyzed. And in indeterminate patients, they all seem to benefit regardless of age, menopause, tumor size.

It is felt that the potential likely use of this, as has been outlined by Dr. Fields, may result in better results than in the restricted blinded study that is presented today.

Certain advantages, which make the potential use of the T-Scan in the clinical setting exciting are those findings of 48 percent fewer missed cancers in the less than

50 year age group. Also, there was a 20 percent fewer negative biopsy rate, which was also significant.

In those equivocal mammograms, it was noted that 27 percent fewer negative biopsies could have been performed and this was highly significant.

Potential T-Scan applications, therefore, seem to be in the area of indeterminate cases, where there tends to be a trend for more positive biopsies for malignant findings, where there can be a decrease in the negative biopsy rate, which, again, was highly significant.

Additionally, this may be especially useful in the age group less than 50, which can be particularly vexing in the diagnosis of breast carcinoma by mammography. Ultimately, the T-Scan could help in the decision process for biopsy versus follow-up.

The T-Scan adjunctive test has benefits when one tends to compare it to -- or potentially benefits when it is compared to a biopsy. Again, in the less than 50 year age group, there is an increased sensitivity and specificity. It has the potential to decrease mammographic postoperative changes that follow open surgical biopsies, which can complicate follow-up. It offers no trauma. It can avoid those postoperative complications that we do see in open

procedures, such as infection, hematoma and pain.

Obviously, the emotional stress is less. Even the minor cosmetic deformities that might follow a benign biopsy could be eliminated, barring those that are obviously worse cosmetic effects, which we do also see.

Certainly, this can be performed in a single clinic visit when the mammogram is performed. The ultimate cost of this should be much less than an open surgical procedure and ultimately we would look into the fact that a -- or would like to see the fact that a reduction in cost could be realized in the overall health care system.

Thank you.

DR. PEARLMAN: Thank you, Dr. Julian, for that presentation.

To conclude our presentation, I would like to speak about the take-home lessons, the conclusions from this study, from the clinical use, as outlined by Dr. Fields and Dr. Julian and the claims and intended use that we are asking your approval for this afternoon.

We have modeled the impact on patient management using a population model starting from 25 million U.S. screening cases and we can investigate this further, if you wish, in the question and answer session. We have aimed

this at the indicated use, as defined in the wording of our indicated use we will give in a minute.

We have incorporated what we believe to be a conservative version of one of many scenarios that we have modeled that represent assumptions based on the findings of the study and in this model, it projects that there would be something in the neighborhood of 6,000 cancers that would be detected by the adjunctive means that would have been missed by mammography alone; that is, 6,000 net.

And concomitantly with this, that there would be some 200,000 fewer biopsies performed in the course of doing this, representing a very significant savings not only in cost, but in trauma to patients. I want to point out that this model -- one of the reasons we call this conservative is it reflects the numbers from the study and not what we believe to be the benefits of targeted use.

Just to put a word on that, in the targeted use study that I mentioned earlier in my presentation that we submitted to you as an -- I think that is an appendix -- by Dr. Laver-Moskowitz(?) in Haifa, the sensitivity and specificity are 80 percent and 74 percent respectively.

The T-Scan in this study by itself had about 70/50. So, that was the significant difference between a

targeted study, where you have an idea of where you are looking, and a blinded screening type of exam read blindly. And, therefore, we believe that in the targeted use mode, outlined by Dr. Fields, that the results would be even significantly better, but even without accounting for that, these are something like the results that might be expected, although any model, of course, can be debated.

The underestimation that I just mentioned relates to the fact that you could not get an optimized placement of the prove. There is no real time usage. This is a very important thing. Those of you who are sonographers obviously are familiar with the importance of that real time feedback, seeing the image, knowing the positioning of the probe, the position of the breast and so forth and knowing where you are to rule out all kinds of artifacts. That is true with this, too. This is a real time system and you don't get any of that benefit from these frozen images recorded by a blinded recording from a tech.

So, we have a lot of false positives in the study that were simply avoidable by proper exam technique in real time that would be the case if this were being done as we are proposing it.

Also, since they were standardized recordings,

there were no high resolution recordings. These were all what we call medium resolution that were used in our screening recording. So, that was not available either.

We had, let's say, moderate training for examiners and readers. We have a program of training that we use for customers outside of the United States today where the product has begun to be marketed. This involves significantly better and more training than we were able to do two years ago starting up this study. So that we think that will also have an impact.

I also want to point out that we did not exclude a single case from this study on the grounds of poor quality, although there were many. The only reason that we excluded a case was if it was incomplete, if it was missing a sector or missing a breast.

In real time use on the patient, you can adjust this as you go. This also would contribute to better results that we got on the study.

Lastly, of course, this is a young technology, not young in terms of the scientific basis of it, but young in terms of its experience as a commercial device. There are many things that are going on that will lead to future improvements in this technology that we expect to improve

its performance beyond this even today.

To summarize then, the intended use for which we are seeking approval is that T-Scan 2000 is indicated for use as an adjunct to mammography for the detection of breast cancer in women. The T-Scan 2000 provides the physician with additional information, which may aid in distinguishing cancerous lesions from benign lesions in patients with indeterminate findings and, thus, to aid in the decision whether to refer to biopsy or to short term follow-up.

Now, I understand that Dr. Sacks is going to be giving a presentation shortly from the FDA and, fortunately, we were privy to some of that. Thank you very much for providing that. And on review of that with him, we have added the following precaution: that patients with mammographic or clinical findings, which clearly indicate either short term follow-up or biopsy may not benefit from the T-Scan adjunctive examination to the same extent as to patients who have indeterminate lesions.

So, with that, I would like to conclude. Thank you for your attention. We like to think that we are seeing the beginning of a new and hopeful addition to the armamentarium of the medical community in the war on breast cancer. We ask your consideration and approval of this

today and we will be happy to answer any of your questions.

Thank you very much.

DR. HALBERG: Thank you.

Unless there are very pressing questions right now, I think we may want to proceed on to Dr. Gamell's FDA presentation and then ask all of the questions at the end. Is that okay with everybody?

Dr. Gamell is the FDA's review team leader for this PMA.

Agenda Item: FDA Presentation of P970033

DR. GAMELL: Good afternoon. I am Paul Gamell, the review team leader.

Today, we are discussing a device to aid in the diagnostic work-up of breast lesions. Our clinician, Dr. Sacks, and a statistician, Stan Lin, will present their review of the clinical studies used to support this submission.

Technological issues, including those of safety, were examined by the review team and do not require input from the panel. These reviewers are available if you have any questions in these areas.

A one volt electrical potential with discrete frequencies between a hundred and 20,000 hertz is applied

between an electrode in the patient's hand, an array of electrodes placed on the breast. The device records a current into each electrode of the 16 by 16 array. These array currents provide the information to produce an image of the electrical properties of the underlying breast tissue.

The density information, including masses, calcifications and architectural distortion seen on a radiograph is directly related to pathology. This has been established through the extensive clinical experience of many investigators.

In vitro experiments in the literature demonstrate the relationship between the changes in electrical impedance and cellular changes. This is not firmly established, however, and is still the subject of ongoing research. Given the current state of the art, the clinical utility is best established by a clinical trial.

These are the indications of use provided by the company. The T-Scan 2000 is indicated for use as an adjunct to mammography for the detection of breast cancer in women. The T-Scan 2000 provides a physician with additional information, which may aid in distinguishing cancerous lesions from benign lesions in patients with indeterminate

findings and, thus, aid in the decision of whether to refer to biopsy or to short term follow-up.

The T-Scan 2000 is designed to be used in hospitals or clinical setting by doctors, nurses or technicians properly trained by an authorized representative of TransScan, Limited.

Dr. Sacks will be discussing the indications for use as part of his clinical presentation. First, we are going to hear from Stan Lin to discuss the statistics.

MR. LIN: Good afternoon.

I will discuss some of the issues that I saw when I did the review of this submission.

An outline of my presentation is as follows: The sponsor's analysis and results will be summarized and then I will go into briefly the original hypothesis for the study, present to you some results on the ROC analysis and some issues and comment and then end with a summary.

This slide here, you have seen much of it during the sponsor's presentation. There were 882 biopsied patients and 1,574 not patients but cases, actually. Depending on the prospective criteria, some of the cases were excluded. There were 481 biopsied patients. Most of them had single biopsy, 458 of them; 23 did have bilateral

biopsy. So, if you take 458 single biopsy plus 23 times 2, which is 46, you get 504 biopsied breasts. That formed the primary analysis data set for this study.

The screening patients, they were used primarily to blind the reader when they did the image reading. Included in this 504, as you have seen, there were 179 malignant cases and 324 benign breasts. One of the things that I noted in my review was that there were 32 percent of the cases had LOS 1 or 2, which are the benign readings on the mammogram. I think Dr. Sacks will have some insight into that issue.

This slide you have already seen from the sponsor's presentation. The only thing I can add is that for LOS 3, it is defined to be probably benign and also defined to be significantly greater than 50 percent chance, but less than 98 percent of the ACR BI-RADS for being benign.

This slide here shows one of the sponsor's main results. By dichotomizing the LOS into test positive and test negative, that is, to biopsy or not to biopsy, the data can be made to show an improved sensitivity from about 39 percent to 51 percent and the sensitivity from 82 percent to 86 percent.

The difference in sensitivity was not significant and when you apply the Metmar test with the specificity, you result in a P value of .0003. But let's look at these results a little more.

The protocol has sought to show a sensitivity in the range of 80 to 85 percent and a specificity in the 70 to 80 percent. What the data showed is that the sensitivity is both for mammography alone and the adjunctive use of mammography, plus T-Scan, achieved this range here. However, neither of the specificities achieved the expected range of 70 to 80 percent.

Now, it might be argued that TransScan was not used precisely the way they would be used in practice. However, whatever that might be, you would have affected both the sensitivity and specificities.

Also, in the protocol, it is stated that the study would include about 200 proven benign cases to provide a confidence interval within 6 percent in the estimation of specificity. Again, this is assumed to be in the range of 70 to 80 percent and that sample size should be able to test the hypothesis to better than -- to less than .01.

The point here is that the actual sample size is 325 for the study, was quite a bit more than the 200 planned

and when that happens, it has the effect of increasing the observed statistical significance. Actually a simple algebraic calculation will show that if one had designed a clinical trial with the significance level alpha and a sample size n, say, and then holding everything else fixed, but doubling the sample size, you would have the dramatic effect of increasing the significance level by orders of magnitude.

That is still true if you increase your sample size by 60 to 65 percent and that if you started out with a small significance level, such as this, the effect is more dramatic. So, therefore, we can summarize to say that the specificity had not achieved the expected range for this study and that some of the effect that you have seen in the small P value, .0003, can be due to a larger sample size than planned.

This slide here shows the other main results that the sponsor had provided. By dichotomizing data again, according to 3, 4, 5 versus 1, 2 LOS, and restricting to those mammo LOS 2 and 3s and calling these now only the indeterminate cases -- there are 273 -- the data will show the sensitivity goes from 60 to 74 and specificity goes from 41 to 57 percent.

Again, if Metmar's test is applied, you would get a P value again precisely of .0003. But notice that I have not put it down on this slide because I wanted to come back and make a comment later.

Just some comments here. The program never defined the indeterminate cases as those with mammo LOS in 2. In fact, it clearly defined the indeterminates as those with mammo LOS 2, 3 and 4s. The protocol never specified the cut point for sensitivity and specificity calculations. That is the business of 3, 4, 5 versus 1, 2.

I am mentioning this because for statistics to work properly, the rules and procedures used for a clinical trial needs to be clearly defined in the protocol because they really form part of the overall hypothesis. Now, only late last week did we receive a fax from the sponsor stating that the dichotomization rule was not stated in the protocol or in the reading instructions to the readers because of clerical error.

Now, the reason why the dichotomization rule was not stated in the protocol might be due to the fact that it was not to be part of the primary hypothesis and, therefore, adequate attention wasn't paid to it at the protocol stage.

This slide here shows what was the primary

hypothesis in the protocol. Throughout the protocol, it said that T-Scan when combined with mammographic findings adjunctively improved the ROC accuracy of cancer diagnosis beyond that of indeterminate mammography; that is, mammogram LOS 2, 3 or 4 in patients referred for biopsy.

So that when you look at this thing here, two things stand out. The one, the primary hypothesis was really on the ROC and that it was to be with those LOS cases 2, 3, 4 on the mammogram.

If one would analyze the results, one should not really just disregard what was the primary hypothesis. The primary hypothesis was on the ROC, was not only stated in the protocol, but also supported by the trial design. The LOS, as you have seen displayed before, were designed to study ROC curves, the receiver operating characteristic curves.

If only sensitivity and specificity were to be compared, then it would seem that the ACR BI-RADS action decision rules would have been adequate for the study.

Before I show you the results on the primary hypothesis, let me show you the ROC analysis for the whole data set.

DR. KOPANS: Can I just ask a quick question?

Are you suggesting that the cut point was a retrospective decision and that can introduce bias?

DR. LIN: Well, what I was saying is that we received the information from the sponsor stating that it was there. It wasn't included in the write-up, but it was implemented during the trial.

DR. KOPANS: But does that introduce bias if -- let's say it was a retrospective stratification? Does that alter the results?

DR. LIN: My view is, as I said, for statistics -- if you want statistics to work properly, things that you do, you go through procedures and they should be clearly identified in the protocol.

DR. KOPANS: Prospective.

DR. LIN: In the prospective.

DR. ALAZRAKI: Can you go back to your slide where you gave the LOS 2, 3, n equals 273, when you showed the change in sensitivity and specificity? Could you go back to that?

DR. LIN: That is the LOS 2, 3 cases, yes.

DR. ALAZRAKI: Yes. But these numbers on this slide are correct. Is that correct?

DR. LIN: These numbers down here are based on if

you restrict your cases to mammo LOS 2 and 3 only, then these are the numbers you get.

DR. ALAZRAKI: And that is correct. That is accurate, right?

DR. LIN: These are accurate numbers.

DR. ALAZRAKI: Okay.

DR. LIN: This is an ROC analysis on the whole data set, meaning that all of the 179 malignant cases and 325 benign cases. This analysis was done according to the software Korac(?) 2, developed by folks over at the University of Chicago and led by Dr. Charles Metz(?). It is a well-known software for this sort of thing.

As you will note that the curves cross between mammography alone and the adjunctively used mammography plus T-Scan, they cross and they are under the curves were not statistically significant different.

Now, the protocol stated that for testing adjunctive use with indeterminate mammograms, cases with LOS 1 or 5 may be excluded from comparison or combination with T-Scan. This is another place that they clearly said that the case were to be 2, 3 and 4s.

If we restrict to our cases to mammo LOS 2, 3 and 4s and look at the empirical ROC plot, you will have for

mammogram 1, two internal points and for the adjunctive use of the mammography and T-Scan, you will still have four internal points.

If we analyze this ROC according to Korac again, this is the result according to Korac. You see again that the two curves cross and mammo is the square 1 and this other one is the adjunctive use of device. The curves cross and the error under the curves are not significantly different again.

Therefore, the primary hypothesis failed to be substantiated and when the curves cross and the errors under them are not different, then it becomes difficult to pursue further because when the primary hypothesis fails, one usually hesitates or don't do -- pursue the secondary hypothesis, especially not for confirmatory purposes.

That seemed to be the case in front of us. Just for information purposes, I dichotomized according to the way it was done before into positivity and negativity by looking at the cases 2, 3 and 4 and there are 297 with 118 malignant cases and 279 benign cases.

You, again, get an estimation within this subgroup now, subset, a sensitivity of 76 percent to 88 percent. And that difference is not statistically different. And, again,

the estimate in this subset of the specificity of 33 percent to 46 percent. Now, note that these two numbers are smaller than the numbers if you looked at 2, 3 only, and those numbers were 41 here, 57 here.

Okay. Again, I have not put down the P value here. In fact, if you do the Metmar's test, you again get precisely the same P value of .0003. This next slide goes into the Metmar's test.

Okay. Because the primary concern is always specificity, so I have shown on this page all the negative cases. As Dr. Buncher pointed out earlier, for Metmar's test, the numbers of concern are in this corner here and this corner here.

For the test, it really doesn't matter what you had over here. Okay. But looking at these corners here and here under mammogram LOS 4 and 5 zero, zero zero and there is a zero here, all zeroes over here. So, if you restrict to any subset according to mammo LOS, let's say 2, 3, when you do the test, 69 goes in and 32 goes in. If you look at 2, 3 and 4, the number that goes in is 69 versus 32 and you can do 2, 3, 4, 5, 1, 2, 3, 4, 1, 2, 3, 4, 5, the whole set. The same number goes in. That is why you get the same P value of .0003.

Now, any one of those is a subset, any one of those dichotomized data, and, therefore, it seems that when one tries to attach a P value to any of the comparisons, care should be exercised. Some caution is to be exercised.

DR. ALAZRAKI: Are you suggesting then that maybe that particular test is not appropriate here?

DR. LIN: The test is appropriate but the thing is that the things you want need to be clearly identified in the protocol because in this case it is just not clear to me what to make of it because no matter how you cut the subsets, you get the same thing.

Okay. Just one or two comments and then I will come to my conclusions.

I just wanted to add one thing to the last slide. The P value of .003, when you try to attach a significance, statistical significance, to the comparison of specificities, remember what I said earlier was that the sample size might be able to explain some of the extent of that small P value.

Okay. Some comments here. Why rely on dichotomization if trial was designed with ratings such as the LOS for this study? And that the ROC value is diagnosting(?) modalities without reliance on

dichotomization of such data.

Okay. Summary. The original intent of the protocol was to show the improved ROC performance for the adjunctive use of TransScan with mammography. As a result, no specific comparison of sensitivity or specificity based on the ROCs or dichotomization of data was clearly specified in the protocol.

The data from the study showed that the ROCs cross and the AUCs were not significantly different between mammography alone and the adjunctive use of mammography with TransScan. This statement is true for the whole data set. Every case is included or if you just look at the 2, 3 and 4s.

That concludes my presentation. I think Dr. Sacks will present some clinical insight to some of the findings.

Agenda Item: Clinical Studies

DR. SACKS: Well, what I am going to try to do here is present from still another angle, point of view, much of what Dr. Lin was just talking about and try to add some things to what the company's presentation showed. I hope by doing it this way that those of you who don't walk around every day and night dreaming ROC curves will maybe get a little more insight in this additional way of looking

at it.

Those of us at the Agency can't escape it. What I am going to particularly spend time on is talking about the expected impact on actual clinical practice and talk about the similarities and differences between the conditions in the clinical trial and those in actual clinical practice, much of which the company has already outlined. And I just want to come back and reemphasize those in somewhat different context.

Now, first of all, the target population will be, I think, a key area in which we are asking the panel's input and asking for some guidance in this particular area. I am going to be stressing what this indeterminate target population consists of that we have heard about and particularly we will be focusing on questions about how to identify this particular subset of the women for whom the TransScan might be clinically useful.

Now, there is one key point here. If what I say now is a little less than clear, it should become clear later when I have some numbers on the screen there. But let me make this point to begin with. If one were to just use such an adjunctive device, any adjunctive device, to mammography, on women who were being recommended for biopsy

and use it only on such women and not on those who were being recommended to wait six months for follow-up for four months or whatever short term follow-up, one would have a problem because the only thing that an adjunctive device could possibly do there is to cause us to miss cancers or at least delay their diagnosis, along with decreasing the number of biopsies of lesions that turn out to be benign.

I never use the phrase "unnecessary biopsies" or "benign biopsies." That is a judgment after the fact. I prefer to use the phrase "biopsies of lesions which turn out to be benign."

So, there are going to be two segments to this target population, one drawn from each recommendation, six month follow-up versus biopsy, and the thing that justifies our combining these two groups into a single target population is inter-reader and intra-reader variability. That is, if I as a radiologist, reading mammography, reading mammograms, were to assign a particular group of women, whose mammograms I read to go to biopsy and another set I would recommend six month follow-up, another radiologist could come in right behind me, take that same set of mammograms and would -- we know from all kinds of studies about inter-reader variability, would be reassigning a lot

of these women from one group to the other and a third reader would reshuffle still again.

That deals with the inter-reader variability. Intra-reader variability is also a bit of a problem, perhaps not as large, but if I were to read those same mammograms a month later, I, indeed, myself might reassign a few of those women.

But in any case, it is predominantly the inter-reader variability that justifies combining these two groups into a single target population. And this is something I will be coming back to again. It is very important to keep in mind.

Now, there is a difference between the trial population and those for whom the device might prove clinically useful in actual clinical practice and that is that the statistics in the trial were done only on the women for whom biopsy was recommended because the company wanted to have a gold standard of pathology, tissue histology; whereas, of course, in actual clinical practice, some of the women, as I said earlier, it would be used on, who would otherwise not be recommended for biopsy.

A difference in the trial conditions, the company has stressed, correctly so, that the separated readings of

the T-Scans and the mammograms is very artificial. Anybody who has done mammography and sonography, for example, knows that you don't do an ultrasound on a breast lesion that you see on a mammogram or that is palpable without having knowledge from the mammogram what quadrant it is in, what part of the clock and help you hunt for this thing because anybody who has done these knows that sometimes these lesions are a little difficult to locate.

Well, the same thing holds with this very similar device in terms of the way you maneuver it in your hand and the fact that it is a live, real time examination. So, that artificiality, I think, the company correctly states understates the effectiveness and that is something that we need to keep in mind here.

Now, I am going to paraphrase the indications for use. I think some of this was written prior to our most recent discussions with the company and the indications for use that they gave you literally should be the ones that you should discuss today and I have no -- this is not in contradiction with those, but this spells it out in a somewhat different way. And that is I am trying to spell out the two groups of women who have to be put together into the target population.

First of all, that the device is intended to be used as an aid in distinguishing cancerous lesions from benign lesions in patients whose mammograms are only moderately suggestive of malignancy but whom it is thought to be prudent to biopsy rather than wait six months for follow-up. These we will recognize as the LOS 3 or the sort of less suspicious portion of the BI-RADS 4 category.

I will have a slide in a minute that will outline the differences between those two scales because I want to iron out any confusion there. That is something that we ought not to let be a stumbling block.

Secondly, the other group, increasing the suspicion and thereby hastening the diagnosis of cancers among lesions which have mammographically relatively benign characteristics and for which it is thought to be safe to wait six months to repeat the mammogram rather than biopsy, these we will recognize as coming from the LOS 2 category of the company or the BI-RADS 3 category.

The words here can be very confusing, and I only put this up just for the sake of completeness, but the next diagram will show us, I think, something that we should keep in mind when we are trying to compare these two scales and I only took this diagram out of the PMA and it is completely

consonant with the verbal description that was given by the company today. But I think it will help to have this.

Now, if we look at this line here from zero to a hundred as a sort of suspicion line, in other words, mammograms down here are those that are -- there is no suspicion for malignancy and those up here, there is very high suspicion for malignancy, then the company's LOS scale, which I have on the top here as opposed to the BI-RAD scale on the bottom, as was pointed out, the LOS 1 is just the zero point; that is, typically benign findings on a mammogram.

The LOS 2 is a very small region here that is, say, in the 0 to 2 percent range of suspicion. That corresponds, as I was saying, to the BI-RADS 3 and, of course, the BI-RADS 1 and 2 are both completely benign. The only distinction between these is whether or not the -- the two, is whether or not there is anything to remark on on the mammogram, such as a mass or calcifications, but which are typically benign and the BI-RADS 1 is that there is completely normal. There is absolutely nothing to comment on.

Going to the other end here first, the company's LOS 5 is roughly coincident with the BI-RADS 5 and it is in

this middle range, where the difference lies. Of course, for the BI-RADS, scale 4 covers the rest. It is a multitude of sins. It is almost a catchall category other than the highly suspicious or hardly suspicious; whereas, the company in order to have a scale that would lend itself more to ROC analysis, just divided that one BI-RADS 4 category into two categories, which ended up being called 3 and 4, with a split somewhere as they pointed out around the 50 percent --

DR. GATSONIS: Can I interrupt for a second?

DR. SACKS: Sure.

DR. GATSONIS: Where in the PMA is this?

DR. SACKS: Page 6-2-26, is it? 29, 6-2-29.

DR. DESTOUET: Dr. Sacks, I also have a question.

DR. SACKS: Sure. Please interrupt me because this is --

DR. DESTOUET: In a standard mammographic factor, at what point is the BI-RADS classification made on the mammogram? Is it on the screening study or is it at the follow-up?

DR. DESTOUET: Okay.

DR. DESTOUET: My question is is the mammogram portion also compromised by giving it BI-RADS 4 before additional views were done?

DR. SACKS: That is right. The BI-RADS category should be assigned after any extra views are done and, indeed, you know, some mammographers actually assign it after an ultrasound may have been done, but it is the final level of suspicion with all of the imaging and, yes, that is absolutely correct.

That, indeed, becomes one of the differences between the conditions and actual clinical practice and in the trial where the blinded re-readings were done by radiologists in the trial, who had no other knowledge about these women, other than their age and, therefore, they are looking merely at mammographic patterns when they assign these numbers.

DR. GATSONIS: So, this is described in the analysis section but is not to be found in the protocol or in the instructions for the readers.

DR. SACKS: This is correct and let me just make one point about the protocol and that is that while it wasn't present in the protocol that was submitted to the FDA, the company has assured us that the cut point between 2 and 3, because this is one of several points I want to make -- the cut point between 2 and 3, which is the same between 3 and 4, where we make a decision commonly to recommend six

month follow-up when it is to the left of this roughly 2 percent area and recommend biopsy if it is anywhere to the right of that is in standard mammographic practice in the U.S. and that was in the instructions to the investigators, but it is --

DR. GATSONIS: Actually, it is not in the reading --

DR. SACKS: Well, that may be. I am going -- when I am done, I am going to let the company deal with that a little more, but we are willing to accept this as a cut point between six month follow-up and biopsy because it is in such standard practice in the U.S. in clinical practice.

DR. GATSONIS: Are you willing to accept that the readers when they interpreted the scans had that in mind? This is the question they would have to deal with.

DR. SACKS: Well, let's hold that one aside and I think that is a very important question. Okay? Let's for the sake -- for the moment, let's assume that is the case and let's come back to that later.

DR. DESTOUET: I have another question about this slide.

The number of cases that you have assigned to each BI-RADS category, as a general rule, Category 3 is the

largest category. Isn't that correct?

DR. SACKS: Oh, these are not meant to be proportional to the numbers of women in them. These are proportional to the level of suspicion on a 1 to 100 scale. The number of women in 1 and 2 is roughly 95 percent of all women screened and the number in BI-RADS 3 is something on the order of 5 or 6 percent, 4 or 5 percent and then a small number fall in the 4 and 5 category. So, these are not proportional to the numbers of women. That is a very good point.

Anything else here before I go on? It is very useful for us to have all of this anchored.

DR. KOPANS: I just want to reinforce, again, what is being said and that is that it is not clear that the readers weren't just given an ROC type analysis, which is the five points and, theoretically, you distribute your readings across those five points. I couldn't find a place also where there was a match-up between LOS and BI-RADS. So, I think that needs to be clarified.

DR. SACKS: Okay. Let's hold that and come back to it. That is one of the things we want the panel's input on.

Now, these are tables. You have seen these

before. It is the same figures that you have seen before and they are in the PMA and I am going to use these tables a lot because I think -- there is no information on the ROC curves that is not on these tables. It is just these exhibit more information explicitly and it is perhaps easier to look at this way. Remember, the top table is for the malignant cases and the bottom table is for the benign cases.

This division, of course, into benign and malignant could not be made until after the fact of the biopsy results came back. What was made ahead of time was whether to assign a woman to -- these are the mammo LOSs, 1, 2, 3, 4, 5 -- whether to assign a woman to column 1, whether it was going to be in one table or the other, column 2. IN other words, you could assign the column ahead of time by looking at the mammogram but you didn't yet know which table the woman should go into until after the fact.

The way I have these shadings different, the light shading -- I have just differentiated the three recommendations -- light shading and LOS 1 normally is normal, come back for routine screening. Two is that number of women who have a very low suspicion of cancer and for whom it is felt safe to wait six months or so, short term

follow-up. That is what has been referred to as short term follow-up. And then everything to the right of this, this whole large area here are those for whom biopsy is recommended.

Again, I have the heavy black line to cut between six month follow-up and biopsy and the numbers at the bottom, the bottom marginal totals here are the numbers of women that fell into each of these columns. There were 13 women with LOS 1, who turned out to have malignancy and 37, who turned out to be benign, but there were a total of 37 plus 15, 50 women in column 1 and so on and so forth for all the other columns.

One other point I want to make about this -- no, let's go on to the next slide and let me show you something. In order to get a grasp on how the adjunctive scores, the 1, 2, 3, 4, 5 come out, it is useful to go through a little exercise here. If the device changed nothing, if it was -- if the mammographic score stayed exactly the same, all of these women, the 13 1s would be up here. They would all be on the diagonal and there would be nothing but zeroes off diagonal. So, the numbers that are the marginal totals would just be up here on the diagonal.

Before you go, Bob, one more point. If the device

were correct every single time, that is, a hundred percent sensitive to cancers in this case, everyone of these -- you remember, the adjunctive scoring rule is to add 1 to the mammographic LOS. If you had 1, that is equivalent to moving down one toward the floor. In other words, something that starts in the 2 column would end up in the 3 row. The adjunctive reading would be a 3, 3 being one greater than 2.

So, anything -- if the device were a hundred percent correct, everyone of these afterward, after being surveyed with the device, the adjunctive would have put a 13 here, a 20 here, a 30 here, a 68 here, and all this would have been 0. You cannot move the 5. That was the scoring rule. If it is already a 5 and you want to add 1, you can't do it. So, it just saturates there.

But all of them would have been moved down if the device were perfect every time. Conversely -- I don't have it here, but the benign chart, the corresponding one, if it were right every time on a benign lesion, then it would have moved everything up one. That is, it would have reduced the LOS score by one to get the adjunctive score. So that a 3 would have ended up in the 2 adjunct. So, everything would have moved up one.

So, I bolded the diagonals here. These are,

again, the original figures, the same figures I showed you two slides back, and you can see, therefore, that these three, which moved down one from the diagonal, were those for whom the device read positive -- these 12 or for whom the device read positive. The 17 moved down one, positive. And so on.

The ones that are above the diagonal are those for whom the device a negative incorrectly. These are malignant cases. So that the LOS read negatively on these two women and their score went from 2 up here, to 1 adjunctively. So that all of these numbers here are the incorrect readings of the device and all of these are the correct readings of the device.

Coming down to this table, the opposite is the case because these are the benign cases. When the device is correct, it tells you to decrease the mammographic LOS by 1, thereby, raising it one towards the ceiling so that if the device -- the device was correct in these 25 women, these 69 women, these 29, these 4, but incorrect in these 30, these 51, these 30 and these 5.

Now, let me point out again something that was pointed out earlier. You have one, two, three, four, five, six women, who are off the diagonal by more than one. How

did that happen if the adjunctive scoring rule is add or subtract one. The answer to that is that the device also in those cases acted like a computerized aided diagnostic device, in which the TransScan read positive but in a different place from where anything had been seen on the mammogram and it caused the radiologists when they did the final two readings of the TransScan and the mammogram together, to go back, re-look at the mammogram and say, oh, my goodness, I missed that lesion. I now have to reassign this woman. I put her in 2, but I see she should have been in 3.

The device is positive. So, that puts us from 3 to 4. So that here are these women in column 2 incorrectly assigned, who went to LOS 4. They really belonged in this column if the radiologists had not missed them.

This woman actually belongs in column 4 here and this one belongs in column 2. This one belongs in column 4.

Now, I am not going to pooh-pooh the usefulness of this device as a CADEX(?) or a CAD, computerized-aided diagnostic device. That is an important second use, but that is dealing with errors of detection by radiologists. We want to separate out the errors of detection from the errors of interpretation.

So, I will later give you a table in which I have moved these women to the right columns, just so we can separate out those effects.

DR. HALBERG: Could you before you leave, for those of us who are not terribly bright --

DR. SACKS: Don't say that. If I could tell you how long it took me to come to grips with these tables, you would think you were very bright, as do I.

DR. HALBERG: Can you summarize how many women who had malignant cases would not have been biopsied on the basis of the adjunctive use of a T-Scan?

DR. SACKS: We will get there. That is where I am going. That is fine. No, that is a great question.

Okay. Now, this, again, is the same table, but I have answered Francine's question with these highlighted numbers here. Remembering that the target population now is going to be just the women who sort of straddle this or border on this cut point between six month follow-up and biopsy, those in close here, the LOS 2s and 3s and in those two columns, these 12 women were picked up by the device while these 8, though, again, because Dr. Buncher pointed out through clerical errors, these were actually only four, and I will adjust for that later, as well, but for the

moment, let's leave it here.

So that of this group of women, 50 women on whom this device was used, there were 12 cancers picked up that would -- that is, there were 12 women recommended for biopsy, who would not otherwise have been recommended for biopsy, but 8 who would have been recommended for biopsy, who were recommended for six month follow-up.

The net effect is 12 minus 8. That is a pickup, a net gain of 4 women, who were sent to biopsy with malignancies. That is an increase in sensitivity. Coming down to the other table, the 60 -- again, target population is just columns 2 and 3 here -- the 69 women for whom the device was negative, when these are the women who did not have malignant lesions, this device was correct.

These are the wins that Dr. Buncher referred to -- 69 women, who would have gone to biopsy were told, no, you don't need to go to biopsy. You go into a 2. That is six month follow-up. Whereas, 30 who would have waited six months were added to the biopsy waiting list and the net effect is 39 -- that is, 69 minus 30 -- saves of lesions -- biopsies of lesions that turned out to benign.

That is an increase in specificity and it is on these figures that the company bases its claim that the

trial demonstrated an increase in sensitivity. That is, 12 is bigger than 8 and an increase in specificity, that is 69 is bigger than 30 and it is very important to keep these things in mind as we go on here.

DR. KOPANS: Can we remember to ask the company how many of those 12 were palpable as well, just as a --

DR. SACKS: Okay. Hold that -- why don't you make a note of that actually.

Now, let's look at the prevalences of cancer. I want to get into the issue of the differences between the trial population and the population in actual clinical practice.

DR. GATSONIS: Is it fair to say that all the previous tables were under the assumption that there is a correspondence between the LOS and receiving biopsy and not biopsy?

DR. SACKS: Absolutely.

DR. GATSONIS: And that assumption is the one that is still --

DR. SACKS: Absolutely.

Now, these are the marginal totals we had at the bottom of those tables. I have just collected them and gotten rid of all of the other numbers so we could see

something about this. These are from the malignant table and these are from the lower benign table.

The prevalences of cancer in each of these LOS columns is, well, 84 percent in the 5 column, not too surprising; 55 percent in the 4 column, not too surprising; about 19 percent in the 3 column, not too surprising; 18 percent in the 2 column. That is surprising and requires an explanation. Let me come back to it -- 26 percent in the 1 column. That, too, requires an explanation.

The explanation in part is that the women who after all -- remember, the 1, 2, 3, 4 and 5 were assigned by radiologists, who knew nothing about this women, did not know whether they had palpable masses, did not know anything but their age. They were looking at a mammographic pattern and on the basis of that pattern alone were asked to assign an LOS and assign these numbers.

Now, how did women whose mammograms look perfectly benign, had nothing on them, end up in a trial for which you had to be on your way to biopsy? Well, clearly, there are many women with mammographic benign mammograms; that is, perfectly normal mammograms, for whom there is a palpable lump and for whom you say base your decision to biopsy not on the mammogram but on the clinical findings. That is what

we can presume in the first instance ends up -- these are the women whose mammograms looked like they were 1s, but they were on their biopsy for non-mammographic reasons.

Similarly, and this becomes far more critical in the 2 column because the 1s are not going to be part of the target population. The 1s and the 5s and, indeed, the 4s -- and we will be talking about that again -- are excluded from the target population. In the 2 column, you have women whose mammograms looked relatively benign. It is the kind of thing that if there was no other information, I would be perfectly happy to wait six months. But, of course, as a mammographer, I never do this without any other information, but that is part of the artificiality of the trial.

These women were, in fact, recommended for biopsy and, again, it was on the basis of non-mammographic criteria; suspicious palpable mass, strong positive family history, high anxiety and unwillingness to wait the six months, perhaps the presence of a gene. One can go on. The point is that there are non-mammographic criteria.

Let me have the next slide for a minute. We will come back to that one.

I am going to site three studies that all demonstrate a particular point here and that is Sickles(?)

in 1991 and 1994 -- and all of these were reported in Radiology and Varis(?) in Uruguay in 1992 -- did a study of when they did, in fact, assign women to six month follow-up. How often were they wrong? How many cancers were they delaying the diagnosis of thereby?

And the prevalence of cancer in those groups, which are the LOS 2 or drawn from the LOS 2 or BI-RADS 3 category was as follows in this right hand column. That is it was very low, less than 2 percent, in particular. This is kind of a well-known fact by mammographers. That is when you decide, you are going to say to a women you can wait six months for follow-up. You are fairly certain of two things; one, that her odds of having cancer are very small, less than about 2 percent and, of course, the other thing, which isn't shown on the slide here is that it will not -- if you do happen to be one of those 1 or 2 percent of women, who happen to have a cancer, we feel that the six month wait will not hurt you.

If we pick up a cancer in six months because we see a little bit of a change, we are fairly confident that you will still catch the cancer early enough to be curable. And, indeed, in all of these cases in these studies, these were women that turned out, you know, to have still the

Stage 1 cancers and not to have been hurt by this.

But that is not the point I want to make. The point I want to make is the less than 2 percent. In order for us to see how this 2 column breaks down, I have made up a way of dividing the LOS 2. This is my own designation. This isn't in the PMA. It is not in the literature. It is just for your pleasure.

Two A and 2B are both based on mammographic criteria; that is, 2A are really on the benign side and I am perfectly confident of waiting six months, recommend that this woman wait six months. She has no non-mammographic reasons to go to biopsy. On the other hand, in 2B, those are the ones where I go home and at 3:00 in the morning, I wake up and I say, gee, I think I had better look at that mammogram again. That one bothers me.

These are the ones I am concerned. I was willing to wait six months this afternoon, but it was the end of the day. I was tired and so on and so forth. The point is that there are those in the two category where I get the willies when I decide I am going to recommend six months.

These are women for whom the device might be useful. Two Cs, these are the women that ended up in the trial. These are the women who have either a 2A or 2B

pattern; that is, it looks relatively benign regardless of whether it is sort of on the A or the B side, but who have other reasons besides mammography, as I mentioned before, to go to biopsy; palpable mass, strong family history, et cetera.

Keeping in mind that and coming back to this table, the LOS 2s that are in the trial are 2Cs. The LOS 2s that this will be used on in clinical practice are definitely not 2Cs. They are 2Bs, because 2Cs will be moved into the 3 category. These are the women who would otherwise be recommended for a biopsy.

So, they are over here and it is on the 2Bs that we will be using this in clinical practice and they don't have a prevalence of 18 percent. The reason the 2Cs have a prevalence of 18 percent is because these are the women who have a higher prevalence of cancer and that is why we moved them in the 3 category in the first place.

So, the conditions of the trial have not included the same women in column 2 that would be used in clinical practice.

So, therefore, when we look at the fact that there were 12 women picked up against 8 missed, these numbers are highly dependent on the size of these numbers down here.

These two numbers, the 30 and the 69 are highly dependent on the size of these two numbers down here and their relative size. And, indeed, the fact that 12 is bigger than 8 is derived from the fact that 20 is relatively large compared to 30 and the fact that 69 overwhelms 30 is that this is relatively large compared to that.

But there are limits on the ratios that these two numbers can have and still have a net gain in sensitivity or a net gain in specificity. Now, what I have done here is I have taken the same tables that we have looked at before and I have just broken down into percents each column. That is, how many equivocals, how many wins, that is, true positives, and how many losses, that is, false negatives.

And of the hundred percent, that is, of the 20 women in this column, 60 percent of them, 12, 60 percent, the device was correct on. These two women, the device was wrong; 12 percent of all the women in column 2, the device was incorrect and so on. You see 57 percent correct, 27 percent incorrect; 68 correct, 25 incorrect. And if you come down to this column, the opposite is the case. When you look at this column here -- I meant when you come down to this table -- in this column, 52 percent, that is, 69 out of 132, the device was correct on. This is, after all,

remember the benign table; 69 percent the LOS -- the TransScan read negative and it was correct, the 52 percent.

It was incorrect in 39 percent. It was correct in 41 over here, incorrect in 54, correct in 27, incorrect in 33. Now, there are a couple of things to point out here. First of all, let's go back up here. There is a lot of fluctuation in these numbers. These are very small numbers, 2, 8, 17. So, 12 percent losses, false negative, 27 percent false negative, 25 percent false negative. Those numbers bounce around a lot.

Similarly, 60, 57, 68 bounces around. So, that one column to another, you get these fluctuations that are somewhat by chance. Likewise down here, the device was correct on all of these, but it was 27 percent, 52 percent, 41 and so on and this one, 33, 39, 54.

Now, it is a peculiarity of the results of the trial that for particularly down on this table we wanted, remember, the 69 to be a big number and the 30 to be a small number for the device to work adjunctively. Well, the 52 percent is the biggest of these three percents and the 33 percent is the smallest of these three. That made this lone number large. That makes this number small.

And over here, this is not -- it doesn't affect

the sensitivity quite as much as it does the specificity. However, I want to point out one other thing and that is what the company has pointed out is the artificiality of the conditions here, that these conditions of separated readings and not being able to have the mammogram in hand when you do the T-Scan and so on is going to badly understate how bad these -- what these figures should look like.

I am going to leave it to the panel to decide what to do about that, but I want to point out that, for example, when we look at 60 percent that the device was correct on, that means that in this column there was a sensitivity of 60 percent. The device was correct on 60 percent of the cancers.

In this column, the sensitivity was 57 percent and as has been pointed out, Dr. Laver(?)-Moskowitz(?) in her paper in -- actually that she presented at the RSNA last year, it was pointed out by the company, she got for the device along a sensitivity of 80 percent and a specificity of 74 percent. The specificity is indicated in this table here, as it was 52 percent; in this column, 41 and 27. So, she got much better results than were gotten here because she had the -- she was using it in actual clinical practice.

These are things that the panel needs to weigh in

trying to decide about these figures. So, these figures do understate. As a matter of fact, you pointed out in the middle of her study they did some electronic improvements on the device and she actually got an increase in specificity from 80 to, I believe, 84 percent and an increase in the specificity from 74 to 75 percent. So, it got even better.

But these clearly understate that. So, while one might argue for statistical purposes, it would be better to average these instead of just taking them where they lie in the particular columns where they lie -- and that would bring this down, but the countervailing point is that this understates to begin with. So, I just decided to leave the figures as they were for the purposes of this analysis.

Now what I have done in this table is I have made the adjustments that I said I would make earlier; that is, I have taken all of those women for whom the device acted like a CADEX, who were here, here and here and put them back in their correct columns; that is, the columns they would have been in by LOS had the radiologists not missed something in the first place. And, furthermore, I gave the company that 4 that Dr. Buncher pointed out. Instead of 8 losses, I put 4 of those back over here in the equivocal column.

Then I recalculated the percentages here. So that

the sensitivity in this column became 72 percent and so on, 59, 68 and in this column here it became 13 percent losses and so on. This became -- instead of 33 percent, it became 34, not much change. The 52 stayed at what it was. But this, of course, was 60 percent in the old table. That is quite an improvement when we make these adjustments and by lowering this to the 4 percent, this used to be in the 20s range and it is now 13.

So, all I have done is just lifted those particular percents so you can just see those and realize, of course, these are true positive. That is incorrect. These are true positives. These are false negatives. Down here is false positives, that should have read, and these are true negatives and we didn't even put all of them in.

Now, I am going to apply those percentages which understate the sensitivity and the specificity of the device used alone, but of course, we are judging it as an adjunct, which I am going to use those percentages as they are on a screening population, with some reasonable assumptions here and I want the panel to challenge these assumptions.

I don't have to invite the company to challenge them.

Twenty-five million women screened each year in

the United States. Let me come down here first. Eight hundred thousand of these women are biopsied. They are predominantly from the LOS 3, 4 and 5. As I pointed out, there are some 1s as well, with palpable masses, but predominately they come in 3s, 4s and 5s, and of these 800,000 women who are biopsied every year, there are approximately 180,000 cancers found. If we say that of the 3s, 4s and 5s, which total 800,000, say, let's assign 300,000 to the LOS 3 category and with a prevalence of roughly 20 percent, 60,000 of those are cancers; 240,000 of those not cancers. These numbers, please, you can play with those. I just want to illustrate the results are dependent on the population.

Going back up to the LOS 2, about 1 1/2 million of these women, which gets back to Dr. Destouet's point, the vast majority are LOS 1s. Okay? So, we are only looking at a small number here. The LOS 2s are about a million and a half, give or take, and the 2Bs, these 1s that -- how do we decide how many of these 2s are 1s that we feel are equivocal? Well, I have taken my lead from Dr. Fields, whom you heard speak earlier, one of the principal investigators for the company.

We had a telephone conference at one point and we

asked how many of those 2s do you feel you have trouble with deciding, lose sleep about and would use the device on and there are several other mammographers on the panel, who might want to, you know, speak to this issue, but I took half in accord with what he thought he would assign to the 2B category and of those, in the 1 to 2 percent range, I put -- as a matter of fact, I took that all the cancers came in this group and that is giving a benefit of a doubt, 20,000 cancers; the other 730,000 benign. And when I put these numbers, 20,000 cancers, 60,000 cancers in 2 and 3; 730,000 benign, 240,000 benign in 2 and 3, we get the next table.

And applying the percentages that I had before, 72 percent, 13 percent, 34 percent and 52 percent and here is the 20,000 cancers. This is in thousands, 20,000 cancers in column 2, 60,000, column 3, the rest, the 730 benigns in column 2, the 240,000 benigns in column 3 and apply those percentages, I get the following numbers of women; 7.8 percent are delayed; that is, they are moved from LOS 3 to LOS 2.

These are the ones who would have gone to biopsy in the absence of a TransScan because they were in column 3 by mammography alone and are told, no, you have no bright spot. You can wait six months; whereas, the device picked

up of women who would have waited six months, the device said, no, you have a bright spot. You need to go biopsy. So, the gain is 14,400 versus loss of 7,800 for a net gain, an increase in sensitivity of 6,600 women. That is 14.4 minus 7.8.

Down here, we have the opposite happening; 125 women who -- these are benign, remember -- in column 3, who would have gone to biopsy are saved having a biopsy and just told that they can wait six months for follow-up. On the other hand, with these numbers, 248,000 of them who would have waited, they are in column 2, six months, are now moved into adjunct 3 and are biopsied. Now, that is a net increase of biopsies by about 123,000. That is a loss of specificity if we use these assumptions.

Now, one might ask the question how small does this number down here have to be in order not to be larger than -- in order for the 248 not to be larger than 125 and cause a decrease in specificity.

The answer is about 360,000 and that would make this 122 and this 125 and then there would be a slight gain in specificity; that is, we would be saving biopsies of more lesions that turn out to be benign than we would be increasing by about 3,000. That is the crossover point.

So, the question then that we are asking the panel is to, you know, deal with figures that one might find are reasonable. Note that the 72 and the 13 understate the efficiency of the device. This number might be in the 80 to 90 range. This number might be much smaller. This number instead of in the 52, maybe in the 74 percent range, as Laver-Moskowitz found and so on.

And that, of course, would affect these tremendously. So, we have to deal with several things. The actual performance of the device, which is shown in the percents here, the sizes of the populations of 2 and 3 that would come into use of the device.

Recognizing that only some of the mammo 2s in a screening practice of all the 25 million women, of the 1 1/2 million who are, say -- who are in column 2, only a portion of those and what portion would the device be used on? Where do we split this 2 for the target population and only those closer to the line go to the TransScan?

Where do we split those that are BI-RADS 4, which, remember, includes 3 and 4; that is, we split it here somewhere. Those that are closer to the line and the other problem, of course, that the panel needs to deal with and that we have been dealing with is how to make the division

between 3 and 4. We must recognize 3s, as opposed to 4s, because if we use the device on people in LOS 4; that is, in the high end of BI-RADS 4, which spans both of these columns, and we say -- if we were to use it on all BI-RADS 4, we would lose not just four cancers here. We would lose 17 more. The device was wrong on these.

And if we were to take a BI-RADS 4 and by the adjunctive scoring rule make a mistake and subtract one from it and get to a BI-RADS 3, which is not what the company is suggesting, you would then be suggesting a six month follow-up and that is 17 plus 4 is 21 women would be delayed by diagnosis versus the 13. You would actually lose sensitivity here. So, the target population boundaries are critical.

You have got to have -- be able to identify and recognize the boundary between 3 and 4 and have to split 2s down the middle, the 2As and 2Bs and stick with the 2Bs. Just to come back and illustrate the same chart I showed before, we have got to split the 2s. Only those closer to this 2, 3 boundary should be used for the device and only those in the lower half of BI-RADS 4 here or so, lower half or so, should go to the device and how to define the boundaries of those populations, as well as the point that

Dr. Gatsonis has raised, how to define the boundary between 2 and 3 itself. Boundaries and target population is the critical issue here.

In summary -- you thought this would never come, didn't you? Maybe you were hoping it wouldn't come because now you have to talk.

One, with the population used in the clinical trial, the company did show a gain in sensitivity and specificity. Two, the device does discriminate between benign and malignant tissue with a frequency better than chance. That was seen in those percents on those tables.

Three, the effectiveness of the device, which is measured in terms of saving biopsies of lesions, which turn out to be benign and/or earlier detection of cancers is partly dependent on the target population for which it is used. This target population must be carefully defined and identifiable by radiologists.

And, lastly, adjunctive use of the device must be judged in the context of the U.S. screening population with the actual prevalences of cancer among women in the various categories of recommendation.

I am sorry -- finally, finally, if radiologists use the BI-RADS scale in the region of higher suspicion

lesions; that is, in that LOS 4 part, rather than the company's LOS scale, the adjunctive sensitivity of the device will be lower than that of mammography alone and that is just illustrated once again to show the ROC curves.

This is the actual data driven one and the last slide is the modeled ROC curve. The problem is the curves cross and what we need -- the 4s and 5s are down in this part of the curve. The 1s, 2s and 3s are up here. The fact of that cross means you have got to stay away from that. You have got to stay in this part of the curve where the adjunctive use has got higher sensitivity and specificity than mammo alone.

If you are operating in this quicksand region here, you actually lose by the adjunctive. It has got lower sensitivity and specificity.

And I thank you for your attention.

DR. HALBERG: Thank you.

At this point, why don't we take a five minute break.

[Brief recess.]

DR. HALBERG: I would like to call the meeting back to order.

I think that with those of us who are here, let's

just start by asking questions of the company.

Agenda Item: Panel Discussion, Recommendations and Vote

Dr. Kopans, do you want to lead the discussion?

DR. KOPANS: Sure.

First of all, having gone through this, I want to congratulate TransScan on the fact that they really, I think, did attempt to do the proper study. I think the only thing that was more daunting in terms of the work that they did was Dr. Sacks' review. I was very impressed with it. I think I understood most of it.

There are, I think, though -- first of all, I think that a prospective blinded study like this is the way to do the proper analysis and I recognize the fact that it does handicap the technology to a certain extent and that is a problem. But I think it was also pointed out that mammography was also handicapped in the sense that additional views weren't obtained.

I have got a series of questions that maybe I will just sort of start and then other people can pick up and then I can ask my other ones.

The concern that I have is that, first of all, I don't think we can say that sensitivity was statistically

significantly increased. So, I have a little bit of problem saying that it detected more cancers. I think that the overall improvement wasn't statistically significant; whereas, specificity was. Of course, we have the problems that are going to be discussed in terms of this break point at 2 and 3 and was that retrospective and artificial and how does that influence things.

But one of the other major concerns I have is the use -- is the involvement of women with palpable lesions and the fact that the cases that moved from an LOS of 2 to an LOS of 3, as we just heard; thereby, increasing the detection of cancers, how many of those were, in fact, palpable and in the face of a negative mammogram would have gone on to have a biopsy.

I am a little concerned that the sensitivity for mammography on the non-palpable lesions was 78 percent in the re-read and, yet, the only way those cancers were found originally had to have been by mammography.

PARTICIPANT: We anticipated that question. There is a transparency with the number of palpable lesions.

DR. BUNCHER: You remember there are 8 lesions that go up and 12 that come down. Of the 8 that go up, 4 were palpable.

DR. KOPANS: So, in a sense, at least -- I am sorry -- 2 were non-palpable?

DR. BUNCHER: Correct.

DR. KOPANS: But 4 were palpable.

DR. BUNCHER: Correct.

DR. KOPANS: So, that meant that the 4 would have gone on to biopsy regardless of the TransScan. Am I reading that right?

DR. BUNCHER: [Comment off microphone.]

DR. KOPANS: Yes. I think -- that is the point that I am trying to make is that it is well-known that a negative mammogram doesn't obviate the need for biopsy in some with a palpable abnormality. So, I think we have to assume -- and maybe I am wrong in the assumption -- that anyone with a palpable lesion that was mammo negative would have gone on to biopsy anyhow in this group.

So, I think that is something we have got to wrestle with and also the fact that the re-reads missed a fairly large percentage of the non-palpable cancers and, again, I would say the non-palpable cancers were the ones that were only picked up by mammography. So, why was there a high -- such a high false negative rate for the non-palpable cancers?

DR. PEARLMAN: I am Andy Pearlman from TransScan.

I would like to ask our mammographers to perhaps comment on the last question.

DR. FIELDS: Scott Fields, Hadassah Hospital.

A patient with a palpable mass is not an indeterminate case. It is very simple. I don't put them in the indeterminate category if they have a palpable mass.

DR. KOPANS: No, no. These were the non-palpable -- when I look at the sensitivity for non-palpable cancers -- and maybe I am reading this wrong -- the sensitivity was 78 percent. So, those weren't -- they are not palpable but, in theory, the mammography reading should have been a hundred percent, although, obviously, it is not going to be with a second reading, but why were 22 percent essentially missed by the second reading of the mammogram when that was the only way those lesions were detected in the first place.

Am I making that clear? It seems to me it is a high rate of miss for a second read.

DR. FIELDS: On the mammogram.

DR. KOPANS: On the mammogram for non-palpable lesions.

DR. ROSSMANN: Dr. Rossmann, Sinai Women's Health.

I think it was very difficult as a reader to read

the mammograms with only two views. The original readers had the benefit of an entire work-up, which included ultrasound, extra views and all the clinical history you could want.

The only answer I can give to you is that we were dealing with, obviously, less than perfect mammogram conditions and, therefore, our readings were less than perfect.

DR. KOPANS: Then can I just ask a corollary question and that is what percentage of the mammograms in the study -- in reading through, it looked like there may be a significant number of mammograms that were not original to the sites, but were outside mammograms. Do you have any percentage of -- in other words, there is no real quality assurance, quality control on the mammograms, although you would like to think that the sites had good quality.

The sense I got was there were a lot of outside mammograms.

DR. PEARLMAN: This is Dr. Pearlman again for TransScan.

It was a minority of -- and I don't have the exact numbers right now, but it was clearly a minority that were from outside institutions we received. There were two

panels formed, PIC(?) 1 and PIC 2, for example, from Allegheny General Hospital that were exclusively --

MR. MONAHAN: Excuse me, Dr. Pearlman, could you get a little bit closer to the microphone.

DR. PEARLMAN: Sorry. Can you hear me now?

MR. MONAHAN: Yes.

DR. PEARLMAN: I said that I don't have the exact numbers right now in front of me, but it was a minority, a clear minority that came from outside institutions in the study. For example, there were two panels, PIC 1 and PIC 2 that were formed exclusively of cases that came from outside of Allegheny Hospital that were referred to Allegheny Hospital and for which we had to get the mammograms back from those other hospitals. That was only 2 out of the 15 panels that we had.

So, I don't know how many others were, but as my recollection serves me well, it was a small minority.

DR. KOPANS: But it wasn't a requirement that they had to have mammograms at the sites?

DR. PEARLMAN: No, no, it wasn't.

DR. ROSSMANN: Dr. Rossmann, Sinai Women's Health.

I think that you purposely -- the company purposely picked sites where there was a lot of primary care

mammography going on. They didn't pick places that had a lot of tertiary referral trade. That is certainly true of the Pittsburgh sites and our site.

DR. KOPANS: So, all those missing mammograms were -- those are missing from your primary sites?

DR. PEARLMAN: There were a couple of sites that tended to be dominant in that, yes.

DR. KOPANS: I have some more questions, but is there anyone else who would like to -- yes, Constantine.

DR. GATSONIS: Can we start by clearing up this issue of the correspondence within the BI-RADS and the LOS? What is the issue -- and the question is like this: The reading of everybody, I think, who went through here, they could not find the correspondence within the BI-RADS and the LOS in the protocol and in the instruction to the reader. So, this must have come to the readers from two different sources. One is through other instructions that are not reflected here or through some kind of decision that the readers made among themselves, that they will interpret the LOS scale in a way that is consonant to the BI-RADS and, in particular, they would interpret the LOS scale to mean that 1 and 2 means no biopsy; 3, 4 and 5 would mean biopsy.

If they haven't done that, then the entire

interpretation that the analysis is putting forward beyond ROC is a problem and, of course, all of the discussion that Dr. Sacks did becomes problematic. So, that is a very key issue at this point.

I will come to the others afterwards.

DR. ROSSMANN: We were instructed each time we read a panel and we read panels -- I particularly read panels on two different weekends, two different occasions. We were instructed of the LOS levels and what they stood for and the fact that the break occurred between 2 and 3.

DR. GATSONIS: And this instruction was just a verbal instruction that happened at the time.

DR. KOPANS: Do you have those written down anywhere.

DR. PEARLMAN: Unfortunately, they were not written into the written instructions but they were given verbally at the sites.

DR. GATSONIS: Just to ask the mammographers on the panel, if you did the dichotomization between 2 and 3, you find some numbers for sensitivity and specificity. Are these numbers consonant with what is being reported generally in the literature? Are these credible numbers?

DR. KOPANS: I guess, I would just -- I would have

trouble knowing what the breakpoint between 2 and 3 was. Maybe you can verbally tell us what the radiologists were -- I mean, what went into the 2 versus what went into 3, because a BI-RADS 3 category, 3 and 4 categories, as we have heard tend to have a range and it is not clear to me how you would break those into 2 and 3 on the LOS scale.

DR. ROSSMANN: Well, the LOS is sort of like -- it is hard to explain -- it is like the lower part -- a 2 is like a 3 and a little bit into the lower part of 4. And a 3 is like the lower part of 4, but not quite as low as the part that 2 has, which I know sounds very confusing. But I think one important part when we were trying to evaluate it was knowing what the break point -- I think when you read a mammogram or at least when I read a mammogram in clinical practice, I have to admit that I look at the film and I decide what I want to do with the patient or if I don't know what to do with the patient and then I admittedly assign a -- in my clinical practice, I admittedly assign a BI-RADS category to it.

I am also trying to think about percentages at that time, but, obviously, you know, a malignant -- possibility of malignancy, because usually your patient is going to ask you that, but I think I jump to what the plan

is going to be. Now, I don't know how other people read them out in the outside, but the people I work with tend to do the same thing.

Then I give it an ACR category.

DR. KOPANS: I am sorry to harp on this, but I think it really is critical.

Did the radiologists get together and discuss what is going to be in categories 2 and 3? For example, BI-RADS category 3, many of us don't agree on what actually goes in there.

DR. ROSSMANN: Right.

DR. KOPANS: So, I am curious to know how -- you know, whether there was any training of the radiologists or agreement among the radiologists because even if this does work, how are you going train people to use it if you don't know which categories actually, which lesions, which lesion types actually go into 2 versus 3? So, it seems to me that is very, very important to have pinned down and to have real definitions as opposed to what is your gut feeling that it is a 25 versus a 26 percenter?

DR. ROSSMANN: I think the clinical application of the T-Scan is getting all confused in these LOS levels, which are admittedly very confusing, but we needed some sort

of number system for the sake of statistics or we couldn't do statistics. In looking at the ACR categories, we had a problem with the fact that 4 was so big that it would be difficult to do an ROC curve with 4 that large.

The way that I perceive this being used in clinical practice, I would look at a case and I would say if I am sure I am going to take this to follow-up, if I have a very strong feeling that this is going to be benign, but I can't a hundred percent be sure, it is going to go to follow-up and I am not going to do a T-Scan on it.

If I am sure this is going to go to biopsy, either I am sure it is malignant or it is just too suspicious looking to not go to biopsy, these are not going to get a T-Scan. What is going to get a T-Scan are the fence -- the ones that you are on the fence about.

Those, to me, occur every day. It is, you know, some of your calcifications that are indeterminate, some of your masses that you would love to call them completely well-defined, but, unfortunately, they are not completely well-defined. They are obscured or maybe they are just not well-defined.

I think that is the clinical application of a T-Scan. So, rather than try to teach somebody in using it to

put them into LOS categories, which as we have all seen is somewhat of a nightmare, I think we have to look at it more on what do you want to do with this patient and do you know what you want to do with this patient. If you don't know what you want to do with this patient, if you want to follow it or you want to do a biopsy, then a T-Scan would be helpful.

DR. ALAZRAKI: Dr. Rossmann, based on your real life situation and how you would use the T-Scan then, is that more -- is that similar, perhaps, to what Dr. Sacks presented with his LOS 2A and 2B levels?

DR. ROSSMANN: Yes. I think if you talk to people who are out in practice -- and let's kind of move over to the BI-RADS system, there is a lot of -- although BI-RADS is defined, say, in the 3 category being 2 percent or less, if you talk to people around the country -- and we did talk in just speaking within these -- to the other readers, it was incredibly obvious how confused everybody is, where some people when you would ask them where does 3 end, they would say 12 percent. Some people said 2 percent. Some people said 7 percent.

This is how they were going back to their particular centers and these were all clinical mammographers

and they were reading mammograms this way.

PARTICIPANT: BI-RADS.

DR. ROSSMANN: BI-RADS 3. And the 4 category they thought was very large and included a huge variance of appearances and people and we did talk to each other and I guess what we realized in talking to each other is that everybody is kind of doing their own thing. I mean, 5s that people seem to agree to very well -- 1s and 2s -- now I am talking about the ACR system -- that isn't a big problem, but the 3s and 4s, there is a lot of fuzzy edges.

DR. ALAZRAKI: Another question, you said you had only two views from the mammograms. Even if the patient had an amplification, you never saw them when you did this. Correct?

DR. ROSSMANN: That is correct.

DR. ALAZRAKI: Why was that? I mean, why was it done that way?

DR. PEARLMAN: This is Dr. Andy Pearlman from TransScan.

As I explained at the beginning, this was so that there would be a standard mammographic set of data to be compared against a standard T-Scan set of data. Also, on the T-Scan, we do not allow use of high resolution close-up

views with the T-Scan. We used a standard screening recording, not targeted.

So, it was felt that in order to have apples and apples to compare, you had to standardize and we would have loved to be able to say that every center on every patient always has the same numbers of compressions and extra views, previous mams, ultrasounds. It depends on the case. It depends on the center, very hard to standardize. So, with some -- obviously, we realized this was a handicap, but it was expressed by our participants in the study that this was the least of evils and the best way to get a truly scientific comparison of the two.

DR. ROMILLY-HARPER: I just have one comment and I really want to compliment you guys and I really think that this whole technology needs to be investigated.

I have a couple of questions. One is that specifically in breast cancer it is notorious to have multiple lesions in the same quadrant of the breast. You can have an area of invasive cancer. You can have an area of DCIS that are all in the same quadrant.

How do you all currently know that the hot spot that you are seeing on the T-Scan image directly correlates to the mammography abnormality? I am wondering if this

couldn't be another reason for a problem with the statistical evaluation.

And, secondly, just addressing the researchers, is there any way to superficially mark these areas that are abnormal and to have some type of depth measurement to determine whether you are dealing with a superficial problem, a deep problem in the breast and how do we exactly correlate that to the mammography?

MR. MONAHAN: Might I suggest that rather than changing places at the table, whoever is answering the question go to the podium. It might be a little bit easier.

DR. FIELDS: Scott Fields, Hadassah Hospital.

It was hard to tell on the slide, but I can actually see through the square that has the active area. You can actually see the skin through that. You can actually look at the skin to it -- it is not completely translucent, but you get an idea and you can see where you are. We have done some pseudo-localizations trying to correlate and now we are doing studies comparing ultrasound in depth, trying to see how we are with depth.

In addition, we are looking at some tissue bath models, seeing what correlates with tissue and what correlates with the electrical impedance, trying to build a

one-to-one histological impedance map. So, we are looking at all these issues.

Depth is an important issue. It can be a problem. We are investigating what is our depth resolution, what is our contrast resolution with this instrument. All these things are being evaluated at this time.

Concerning multi-focal or multi-centric lesions, because we don't have at the current time an instrument which can do a biopsy on the basis of the T-Scan, that can be a problem, but the company is working on a device to do T-Scan localizations. It turns out if you put a needle in and when you hit the lesion, it acts like a little antenna.

So, that is being worked on as well. Hopefully, that will be out sometime.

DR. KOPANS: Couldn't you put a needle straight down where the lesion was toward the chest wall carefully and then the mammogram would see what the needle had transfixed?

DR. FIELDS: Actually, I advised the company to do that, like some of the old ultrasound-guided probes. When the needle would hit the lesion, you get this very strong signal. They are working on a different model. It can be done. It will be done sometime in the future.

DR. DESTOUET: Dr. Fields, you say that you use this modality in an anatomical mode and I didn't quite understand what that meant.

DR. FIELDS: It wasn't shown on many of the slides, but there is the standard nine sector examination of the breast and there is also the anatomical model, where we put it wherever we want and we indicate on the screen -- we put a little indicator where we recorded the signal so we can actually record it in a multitude of positions. It is actually -- free hand, basically. It is not in the standard nine sector mode. It is called the anatomical mode.

DR. DESTOUET: Like real time imaging?

DR. FIELDS: Like real time imaging. Precisely.

DR. DESTOUET: Do you have any data on the number of patients you have done mammography on and then the T-Scan on and there has been a change in the management of those patients either toward biopsy or away from biopsy and what the -- I am actually asking what the positive predictive value and negative predictive value is?

DR. FIELDS: Since the completion of the study, we have done some on the order of 250, possibly 300, patients. I don't have data on that. I can only tell you that my confidence level has increased. I haven't missed a cancer

since the completion of the study, to my knowledge.

DR. DESTOUET: Do you use ultrasound in your practice?

DR. FIELDS: I have ultrasound in my practice, sure.

DR. DESTOUET: What is your usual algorithm then for evaluating either a symptomatic patient or an abnormal screening mammogram with mammography, ultrasound and T-Scan?

DR. FIELDS: I use everything I have. I tend to use the T-Scan last because I am particularly interested in seeing where that falls in because I have to have a -- I like to have an interdeterminate patient. If I did a T-Scan first after the mammography, before I might do an ultrasound, that kind of obscures how I feel about the T-Scan. So, I tend to use the T-Scan last. It also depends on what is available. If the ultrasound room is busy, then I might do the T-Scan first, but certainly what I like to do is the mammography with all available compression views and all available extra views that I might want to do, followed by ultrasound, followed by T-Scan would be the general order of things --

DR. DESTOUET: But you don't have any prospective data on the breakdown of each of these?

DR. FIELDS: No. We only finished the study sometime in the late spring. So, it is kind of early. We only have a few patients with follow-up.

DR. DESTOUET: And depth of lesion, there was -- we don't have any data on good the T-Scan performed in depth of lesion, depth of cancers in the breast -- do we have any data on that.

DR. PEARLMAN: Dr. Andy Pearlman from TransScan.

We don't have a large enough set of data to make statistically significant claims, but I can tell you that in the study, as you saw from the example that Dr. Field showed, we had lesions all the way at the chest wall and every part of the breast picked up -- what matters in this device is getting the probe close to the lesion. Since the breast is highly mobile and you can orient the breast and compress it in our device in many different angles, you can end up even with lesions that in the free breast are deep, end up being close to the probe. So that --

DR. DESTOUET: What if you have a large breast, though?

DR. PEARLMAN: In large breasts also. We saw that --

DR. DESTOUET: Even in large breasts, you can get

close enough to --

DR. PEARLMAN: Yes. And you saw that in the analysis of our data that the sensitivity and specificity for large breasts was almost identical to that of all the other ones.

DR. DESTOUET: The number of introductile cancers, I am not quite sure how many were detected with the T-Scan did you break down?

DR. PEARLMAN: We don't have that data yet but there were a large chunk of cancers that were detected that were introductile.

DR. DESTOUET: A large chunk.

And cancers under a centimeter, do we have any --

DR. PEARLMAN: Sure. We have that breakdown. Forty-five percent were below 1 centimeter.

DR. DESTOUET: Of cancers, not tumors.

DR. PEARLMAN: Cancers.

DR. DESTOUET: Thank you.

DR. SMATHERS: You mentioned in the write-up and everywhere that you have this high resolution mode. Does anyone ever use it and, if so, how much more time does it take over the standard resolution mode?

DR. PEARLMAN: I will first make just a comment

about the last part of that question. This is Dr. Pearlman again.

It doesn't take anymore time at all. It is simply that in order to do it, you cannot do -- excuse me -- I want to correct myself on that -- to do a sweep of frequencies takes longer on the high resolution mode than in the low resolution mode. That is correct. That is the reason why it wasn't used routinely for the scanning of the nine sectors because it would simply prolong the recording beyond reasonable time.

That has now been speeded up in the new system that we can now offer. And we believe that that will be more practical and usable. However, in a study it was not practical to do that on all the patients. That is why we standardized on the medium resolution.

DR. SMATHERS: Appreciate that. Is anyone currently using it clinically? The physicians that are using the machine right now, are you using it in normal mode or high res mode?

DR. FIELDS: I use it in normal mode. When I see a lesion, I will look at it with high resolution to see if it looks any different, to see if it is more clear, more definite. But in an analogous mode to a magnification view,

we use a magnification view. If it is more suspicious or less suspicious, it tends to push us in one direction or the other, very similarly with the high resolution mode.

DR. SMATHERS: Does the detectibility sensitivity improve with the high res mode?

DR. FIELDS: No. I only use it if I see a lesion in the normal mode.

DR. KOPANS: Dr. Fields, I just -- and also in terms of the study, what do you do if T-Scan is positive and everything else is negative, clinical and mammographic?

DR. FIELDS: In the study or currently?

DR. KOPANS: Well, both.

DR. FIELDS: In the study we have had patients -- there are patients that were T-Scan positive and other things negative. According to the Helsinki Agreement, where I work, and other agreements, institutional use or whatever it is called here, we cannot use this data to affect the patient's management in a clinical trial. That is the law.

Should this device be approved for clinical use, we will have to go back and review these patients and get a hold of them and see what is going on. Currently, we are investigating those patients that have hot spots in areas that are not physically or mammographically abnormal and we

are investigating why those are.

On many of them, we are investigating the time of the menstrual cycle. We are investigating other possibilities as to what might be a false positive. We are getting these patients back -- some of the patients, we have had them back two weeks later and the lesion is gone. So, some of these might be affected by menstrual cycle.

DR. ALAZRAKI: In the demonstration and some of the earliest pictures that you showed us, you showed that I think it was four quadrants and you accepted the lesion as being related to the mammographically identified lesion if it appeared in any one of those four quadrants in the region of the mammographic lesion. Am I correct? Yes.

But, in fact, many of those T-Scan lesions that you saw looked to be quite distant from where you would have thought the mammographic lesion would have been. How do you know that those are not some of the things that you are talking about now that might have disappeared if it had been repeated in three weeks or two weeks?

DR. FIELDS: Well, the study was the study and real life is real life. I didn't design the studies. I would have liked a little bit -- I would have liked it to be a little bit more stricter, perhaps, but, again, we didn't

have the anatomical mode in the study. In a clinical practice, we have to be a little bit more careful as to where the lesion is on the mammogram, as to where we see it on the T-Scan.

Does that answer your question?

DR. ALAZRAKI: I guess, as well as it can be answered.

Do you have any -- are we allowed to or supposed to or not allowed to ask about costs of tests here?

MR. MONAHAN: I think just in general terms it might be appropriate.

DR. ALAZRAKI: In general terms, how do you think a T-Scan test in terms of the charges or costs would relate to the cost of a biopsy, let's say?

DR. PEARLMAN: This is Dr. Andy Pearlman from TransScan.

We are investigating costing, but it appears from our experience in other countries where this is being done, that the cost of the T-Scan adjunctive exam is way below that of a biopsy, even way below that of a needle biopsy and even lower than that of ultrasound.

MR. MONAHAN: I would point out that in making your decisions today in your voting, it is not relevant.

DR. KOPANS: I would like to go back to the lesions that really this seems to make a difference, the 2s and the 3s. Have you gone back and looked at the 30 cancers that were classified by the re-read as 1s and 2s? Actually, the 2s would be the ones that shifted on mammography to see, you know, what kind of lesions those were. Were they, as Dr. Sacks suggested, just a visual error or were they subscribed cancers, for example, that the reader may legitimately have classified them as a 2?

And just one other question and that is -- I assume lobular carcinoma in situ was not counted as a cancer. Is that correct? So, it was just invasive ductile, invasive lobular and ductile carcinoma in situ. It would be nice if we could get a breakdown of those lesions and then also a redo of the data on the various sensitivities and so on for size for non-palpables alone. They are grouped, but they are not broken down by the sizes.

DR. PEARLMAN: This is Dr. Pearlman again.

Those are excellent suggestions and we can do some of that analysis.

I just wanted to make a comment about the comparison of the LOS 2s and 3s and the switches between them. I think Dr. Sacks made a very good point, that there

is a significant amount of inter-reader variability in the mammographic reading by itself.

As a matter of fact, we did compare readers. It was in your submission on I think it is Table 24 or 25. But the inter-reader variability on the mammography was far greater than the -- I shouldn't say far greater -- it was greater than the inter-reader variability on the adjunctive read. It actually reduced it somewhat.

In looking at why was it that the original mammographer called it a biopsy and, yet, it was re-read as an LOS 2 by the re-reader, you can also compare what did the second re-reader say about the same case.

There was a significant inter-reader variability such that I am not sure that you can learn an awful lot from this fact that some of these cases were read by one as a 2 and one as a 3. There is a significant inter-reader variability in mammography, especially in the indeterminate cases.

DR. KOPANS: Sure. But I guess where I am heading is that if you had defined, you know, what is LOS 1, 2, 3, 4 and 5, presumably it would have been a descriptive definition. We are going to put all circumscribed masses in LOS 2 or LOS 1. We are going to put all dilated ducts as

LOS -- I mean, you know, I could see how you could define -- so, at least you would have -- the problem that I have is that there is -- what would a practitioner be using to place these cases. The big concern I have here is that the negative predictive value, if I have got this right is about 87 percent, which is pretty good. But that still leaves me with a 13 percent error rate.

If I am sitting on a case where this could be wrong in 13 percent of the women, my belief is that most people would opt for a biopsy anyhow. So, how do you -- you know, without specifics, how do you -- how can you sit on a 13 percent error?

DR. PEARLMAN: Dr. Pearlman from TransScan again.

The negative predictive value of the test was 87, which was higher than that for the mammography by itself. It was significantly higher than that for mammography by itself. Obviously, some patients are not referred to biopsy, who are on the borderline. They are referred to follow-up. A mammographer makes a decision based on the best information they have.

The question is whether the additional information that this offers increases the confidence of that decision to follow-up or to biopsy in those patients. That is

basically, I think, what our clinicians are saying, that both in the study and in real target practice, as -- I should say in targeted use, such as Dr. Fields has described, this is the case.

Also, bear in mind what Dr. Sacks pointed out, that these figures, such as the 87 percent negative predictive value, are based on the study, which did not take advantage of all of the things that we talked about, based on the real time targeted exam that can give you a higher confidence level of what the T-Scan is saying.

I think that it needs to be reevaluated in a -- as we go forward and we use this in clinical practice in the adjunctive mode to see if the negative predictive value is, in fact, higher than that.

DR. KOPANS: I apologize for doing this, but I think it is often telling. Let's say the negative predictive value is up to 95 percent. Is that maybe -- that would be reasonable in practice. If it is your wife and presumably you love her, would you rely on the T-Scan?

That may be rhetorical, but it certainly is something to think about.

DR. FIELDS: It is something to think about even without the T-Scan.

These are clinical judgments. On my flow chart, I had some typical things, which might be in an indeterminate mode, which might point to an indeterminate category. I understand the next version of BI-RADS will have some of these image characteristics to guide the radiologists into putting cases into individual BI-RADS categories.

We might be able to do that, but at the end of the day, it is still a clinical decision on the basis of all the information. No decision is made on the basis solely of the T-Scan. It is made on the basis of all the information, not on the basis of a T-Scan alone. That is how we make the decisions.

DR. GATSONIS: Let me try to get us back to more prosaic issues, like getting through this evaluation of the data. The question that we started addressing earlier about what was the cut point that the radiologists had in their mind does not refer to what the radiologists would do from here on. It refers only to what they had in mind when they were reading the scans.

Hence, the discussion that Dr. Rossmann was saying, to me, does not address the issue. The issue was when the radiologists were making the particular calls in the study, did they have in mind that a 1 and 2 meant no

biopsy and a 3, 4 and 5 meant, yes, biopsy. If they had that in mind, I am willing to go on for that. This is the issue that makes it possible for you to do a credible analysis of sensitivity and specificity. Because if I move the cut point and I put the 3s with the 2s, then the whole picture is backwards and nobody should put in the trash can.

DR. ROSSMANN: The answer is "yes," we have the cut point in mind.

DR. GATSONIS: Okay. Fine.

The next --

DR. BUNCHER: I would like to go one step further than that. We discussed the results with the FDA in February when only half the data were in and we were using the 2, 3 cut point at that point. I mean, we had already established that in our mind.

DR. GATSONIS: You had established it, but the readers had it as well.

DR. BUNCHER: Then they had established -- the reason we had established it is because the readers were using it.

DR. GATSONIS: Right. That is -- so, at that point then you decided to abandon the ROC analysis.

DR. BUNCHER: No. We abandoned the ROC analysis

before that. My optimistic colleagues came in and, obviously, thought the new device would supersede all previous devices, as most folks do, and we explained to them the sample size is required to show what would be necessary in order to prove that and then we went on to the idea of using it as an adjunctive mode.

Is that where we were at?

DR. GATSONIS: I see. And, hence, then, the whole discussion about using the ROC to compare and so on, then is not really relevant for what you want to make of this for the future substrate.

DR. PEARLMAN: There is one other reason that we wanted to use an ROC curve. That was the other hypothesis of the study was does T-Scan detect cancer by itself better than chance. And for that, we were instructed to construct an ROC curve.

DR. GATSONIS: Just for the record, for the ROCs that you have, if you have identified in advance a region of specificity that is more of interest, you could have looked at partial areas under the ROC curve. That is something that if you specify in advance you could do and you will not get into some of the problems that have to do with the arbitrary choice of cut points later on.

I did not notice such a -- I had one question also, a technical question about the ROC. At some point, you say in the PMA material that in the region where the ROCs for TransScan was higher than the other, when you did the confidence intervals on the ROCs, they did not overlap.

Now, I re-did those calculations and I couldn't verify that. Is that true? In other words, the ROCs in that part, despite the fact that one was above the other, they still seemed to overlap to me. But I mean, I did these quickly. You had the data in front of you for a long time.

Just some clarity on that because this will also get you to the issue of whether the ROCs are really separate even at that point. So, just to make the general point now, on the basis of the ROC analysis, it is a wash. The comparison is a wash unless some other data come to mind.

The next -- excuse me -- yes, I wasn't asking a question, but please.

DR. PEARLMAN: This is Dr. Pearlman from TransScan.

I just wanted to comment that in the ROC modeling that we did, it was using, I believe, a binomial model to fit the data.

DR. GATSONIS: A binomial model, yes.

DR. PEARLMAN: And the fit was not particularly near the data points.

DR. GATSONIS: It wasn't very good. I agree with you.

DR. PEARLMAN: And because of that, it tended to underestimate the difference, even in the area of concern. In other words, it is not only that it was getting the entire curve and the entire curve didn't add up to a net difference because it crossed at some point, but even in the area above the cross, where it is effective, it is underestimating the difference because it is basically a lousy numerical model of the data.

DR. GATSONIS: It is a binomial and then you can criticize the model, et cetera, et cetera.

Just a related question I had to the ROC analysis, is the adequacy of the gold standard. Some women had a core needle biopsy. Some women had surgical biopsy. Some had F&A. Do you have a breakdown of that? F&As, my personal bias, are not very believable these days. I will say that on record, but that is just my bias.

DR. FIELDS: We didn't use F&A data. It was only histological or core data or open biopsy. F&As were not accepted.

DR. GATSONIS: I must have misread then. I apologize. I thought that there was a mention of F&A in there.

DR. PEARLMAN: There were cases in which an F&A was performed and as a result of that, an open biopsy was performed and we used the open biopsy data.

DR. SMATHERS: To change the tenor just a little bit, I noticed in the -- well, what I noticed was an absence in the documentation. At least, I missed it, it is there. Have any calibration phantom or any daily quality assurance program for the device that would allow it to be checked out each day to be sure it is working properly.

DR. PEARLMAN: Thank you for raising that question.

The device is an impedance measuring device. If you will, it is sort of like a very large multi-channeled biometer. We have built into the device a standard bed of resistors and capacitors that are used to calibrate the device. Every time you turn it on, it runs through a self-test. It reports if it fails directly to the user and won't let them go on. So, there are tolerances built into it. It checks itself every time it is used.

DR. SMATHERS: What about resolution factors?

DR. PEARLMAN: Well, the resolution on the measurement is determined by the resolution in the impedance measurement itself. In other words, what is the percentage of plus or minus error about the estimate of resistance or capacitance at a given frequency in each sensor in a system. That is what determines the resolution of a system and that is measured against an internal calibration standard.

DR. SMATHERS: You are using this clinically and you should be able to see a given artifact at a given depth in a breast. I assume you could see the same thing in a block of gelatin.

DR. PEARLMAN: We haven't done -- in fact, done water bath type experiments in which we have measured the depths to which we can detect an object of a known impedance from its surrounding of a different -- of a known diameter. Those studies show that approximately 2 1/2 to 3 times the diameter of the object is the limit in the present system that we can detect and that is what we found when we did these bath studies. Now, in the actual measurements that we are doing in the body, again, the measurement is done by compression orientation of the breast, such that the actual distance from the sensor to the lesion is a variable, dependent upon many different factors.

It is not just the apparent position of the object in the mammogram or in the free breast.

DR. SMATHERS: So then in a 3 millimeter lesion, you wouldn't be able to see if it were more than 9 millimeters from the surface of the skin.

DR. PEARLMAN: That is a theoretical statement based on water bath experiments, but there is definitely an importance of proximity if you happen to probe close. I can say that as a biophysicist who has done modeling of things like this in the past, I know that it is tempting to draw conclusions from simple water bath type experiments into the body, but, obviously, things will get a little more complicated when you have a non-homogeneous medium and you are trying to extrapolate results from the homogeneous ones.

DR. SMATHERS: And I would say that for a 3 millimeter lesion, 9 millimeters in optimum depth, and it might be less.

DR. PEARLMAN: Yes, but I want to point out that in actual practice in use of this device, the typical thickness of the layer of skin left after you have oriented the patient so that the breast is hanging away from the skeleton, applied pressure at an angle using the probe it is not much more than that typically.

The fact is that we see bone through the -- in the image in many cases.

DR. DESTOUET: As a follow-up to what you just said, Dr. Laver-Moskowitz in her pilot study said that one particularly large lesion was missed with the T-Scan and that in general, large tumors have a less striking appearance than small tumors. What you have just said, I don't understand.

DR. PEARLMAN: That is a different phenomenon that is being referred to and that has to do with the histological make-up of the tumor that you are detecting. A small fast-growing tumor has a different amount of fibrous tissue, for example, than, say, a large, older tumor. And we are detecting a net impedance difference of the total object from its surroundings so that if you have, for example, a fast growing area surrounded by fibrous tissue or by fat and it is a small area, it gets averaged together and looks like a less striking difference than it would otherwise be.

In a fast-growing tissue, a small lesion, it is very distinct from the impedance properties of its surroundings. In a highly diverse structured lesion that could have fast-growing areas and fibrous areas and it is

all mixed together, it could have a different appearance.

What I am saying is based on histological studies that have been done in other centers, but we are at the present time investigating all of these properties to try to understand them better. We do have studies planned for follow-up. This is not our last study by any means. We are continuing to investigate this technology.

I just want to mention that one of the things that we are planning to do and we are discussing this right now with several U.S. sites is an ultrasound-guided needle biopsy study in which we have the lesion identified in real time while you are looking at it, so that before they do the needle biopsy under ultrasound guidance, the T-Scan is recorded of that lesion.

That would give us lesion specificity. You are asking a question about how can we know -- that would give us lesion specificity. You are asking a question about how can we know that it is the same -- that would give us absolute certainty as to the lesion. It will also give us some depth information.

DR. HACKNEY: This is a comment, but I hope you can reassure me about the concerns. You have explained very well why you did the study the way you did and I think many

of the rationales make sense. The problem is that you have ended up with a situation in which you artificially depressed the diagnostic performance of mammography and you assume you have artificially depressed the diagnostic performance of the T-Scan.

Neither of them have been compared to the totality of the clinical picture that was used in clinical decision-making in these patients. The assumption is that to whatever extent the diagnostic performance of both techniques was depressed, that the relationship between them would be the same if you used the totality of clinical information.

But we don't have any idea of whether that assumption is true. Particularly, we don't know whether the true mammography with knowledge of the clinical presentation, with evaluation of the patient, with an examination of the breast would have resulted in every case that the T-Scan picked up in the adjunctive study, being picked up on clinical grounds instead, so we don't really know whether in those patients the T-Scan actually contributed anything. We also don't know whether there is cases in which the T-Scan suggested this is less likely to be malignant would have been believed to have been less

likely to be malignant or at least avoided biopsy in the totality of the clinical information.

So, while I understand how you ended up in this situation, I find it very difficult to extrapolate from this situation to the application that is being proposed, which is in the patient in whom the totality of the clinical situation is unclear and there is a decision to be made whether to biopsy, whether adding a T-Scan to that, not just to two views of a mammogram, but to all of the information that is available, will actually result in a better diagnostic performance.

I think it would be possible to do a study in which you get closer to that. You might even be able to get a bit closer to that by reanalyzing your data and telling us what happened with the follow-up patient, with the patients who did not get biopsies. But as it stands, there are too many leaps of faith for me to feel comfortable with it.

DR. PEARLMAN: Before I pass this to the docs for comment, I just want to make a statistical comment. You are raising a very valid point and perhaps to give you an idea of a direction for a solution here, if you look at the overall performance of the mammography in the re-read, it was 82 percent sensitivity, 39 percent specificity.

How does that compare to published figures from the field? I think that is not too far off from accepted mammographic sensitivity and specificity. The T-Scan in the same study had about, I think it was 68 percent sensitivity and 45 or 46 percent specificity. Now, that is to be contrasted with the results of the Laver-Moskowitz study on nearly 300 biopsies in which she got 80 percent sensitivity and 74 percent specificity.

If you look at the difference in the performance of the T-Scan in the one versus the other, it is very dramatic; whereas, I don't know if you can find a comparable change in mammography performance by adding these other things. I don't know.

Now, I would ask my clinicians from the clinical standpoint to speak to how can they have confidence that this can, in fact, be useful in --

DR. HACKNEY: Just before you do, I think that is part of the problem is you are forced to compare T-Scan plus mammography to mammography alone, rather than T-Scan plus mammography plus clinical evaluation to T-Scan to mammography and clinical evaluation alone.

The question is whether these cases that the T-Scan is doing better than mammography alone, mammography

plus clinical evaluation is assumed, believed, to do better than mammography alone. Are we actually gaining anything if we do the experiment that wasn't done, which is add T-Scan to the total clinical information, which includes mammography, but is not restricted to mammography?

DR. KOPANS: In particular, though, just to add to that before you answer, you have included clinically detected lesions and yet you excluded the clinical information. I think if you -- I would like to see the data redone with just mammographically detected lesions. I think that would eliminate at least the issue of the palpable lesion.

And just one caveat and that is that the sensitivities and specificities that were just quoted are -- don't forget you have mixed in screening asymptomatic women into your mix. So, I don't think we can talk about sensitivity and specificity for mammography in that particular context because you don't know what it is. It depends on the mix of normals that you have got in there. So, be careful extrapolating from those figures.

DR. PEARLMAN: Could I just follow up with Dr. Kopans on that?

Would you feel that from 80 to 39, that there

would be anticipated a very significant improvement if mammography in the same cases were read in light of all kinds of other data, like additional views on compression and so forth?

DR. KOPANS: I don't know the answer to that. Don't forget, the specificity for mammography and screening is like 95 percent. So, you have thrown in some 95 percenters in there into your mix of biopsied lesions. I don't know. I would have to really think and I don't know if you could actually figure out what the sensitivity and specificity of mammography would be.

In defense of what you have done, I think it is the -- you didn't quite go far enough but I think it was the right thing to have blinded interpretations of the mammogram, blinded interpretations of the T-Scans. I think by having clinically suspiciously -- or clinical instigated biopsies, you threw in another level of complexity and didn't account for it by having the clinical information as well.

So that it might be if you could go back and look at the data, knowing where the clinical abnormality was -- of course, you didn't have a grading of the clinical abnormality, but I think maybe eliminating the clinically

suspicious abnormalities and redoing the data, as I suggested earlier, could get around that. You don't get around the issues of spot compression and so on, but, you know, mammography in a screening situation, which is sort of what you were doing in your second read of the non-palpable lesions, you wouldn't get extra views, unless you saw it in the first place.

So, you might again be able to answer some of those issues not optimally but without too much pain by eliminating again the clinically evident lesions.

DR. PEARLMAN: One more comment. Again, on the non-palpable lesions, the improvement in specificity was from 41 percent to 51 percent, which was a P value of .025.

DR. KOPANS: But, again, look at the shift of lesions. Again, that is my -- my major concern is shifting a lesion from suspicious to, you know, follow it up. I think, you know, that is really to me the crux of the issue. I think moving it from an LOS 2 to an LOS 3 is also important but I don't know how that -- I guess you did have those data. I would like to look at them again for the non-palpables. It seems to me there were only two lesions that were non-palpable, as opposed to eight that got shifted. I would have to look at that again.

For the non-palpables only is what I was asking about.

DR. FIELDS: Scott Fields.

I just want to comment on Dr. Hackney's point. At the end of the day, it is not only our sensitivities and specificities, but in the larger picture, the question is will there be less women dying of breast cancer because the T-Scan exists or is available. It is not only the sensitivity, but what happens in a larger sense. That study can take 5, 10, 15 years. I would be happy to do a HIP or BCDDP impedance study, but that is a very long study. But that is actually the bottom line, not if we have raised our sensitivity or specificity to certain levels.

DR. KOPANS: There was one other point that I wanted to come back to and that had to do with Dr. Sacks. Maybe you could comment again, the issue of shifting the cut point in terms of shifting -- actually making things worse.

You know, how do you feel about that in terms of what you have heard about what the readers were told to do? You mentioned that if you shift the cut point to 3 to 4, then you might actually shift things dramatically in the other direction.

DR. SACKS: This table should help in this

discussion. The whole problem lies in trying to find three boundary lines, just to summarize this again. One is, of course, where is the cut point between 2 and 3 and I think the company has answered that in that this is the decision cut point between women that I would have had wait six months and women whom I would have recommended biopsy for in the absence of a TransScan. I don't have any particular problems with that.

The issue is how to define the boundary that cuts down the middle of the 2s on whom this would be used in clinical practice and to make sure that we stay away from the high edge of the BI-RADS 4s or LOS 4s because of too much loss of sensitivity.

Now, both Dr. Rossmann and Dr. Fields have said that the people on whom they would use this -- and this is very reasonable -- is the women on whom they are having trouble deciding which side of this line to put them. The question that I don't know how to answer from the clinical study is for each radiologist, they may have a different -- suppose you took all the women that Dr. Rossmann, for example, in the absence of a TransScan, would say, gee, these are the women that I don't know whether to put them on 2 or 3. Suppose we weigh it until we had a hundred such

women. The question I would have is how many of them would she actually have put on the 2 side and how many on the 3 side. In other words, what is the relative size of these columns, that is, the total here and here, if the TransScan weren't around? And without knowing that -- you know, I have talked with Dr. Pearlman and we have talked about different models and we have talked about that approximately 3 to 1 is the cut point here, about 1 in 3 are -- 1 in 4 are placed on the 2 side and 3 out of the 4 in this indeterminate category of indecision are placed on the recommend for biopsy side, which may be reasonable.

I am not sure what it would be in my practice. I have no idea and it may vary tremendously from one radiologist to the next. So, we don't know really how to assign the relative numbers here and here, which make all the difference in the world in determining whether this number is larger or smaller than this one and, likewise, whether this number is larger or smaller than that one because those are the only ones that count.

This is where I am asking the panel to, you know, help us and the company, indeed, to help us figure out, you know, is this going to have even a greater inter-reader variation. If one reader is extremely conservative and in

the cases they have problems deciding, they put 90 percent over here and only 10 percent over here in the absence of a TransScan -- and that is what counts here -- then, in fact, this number will get much larger and they might lose if they use the TransScan on those people, a sensitivity and although they will gain tremendous in specificity because this number will be much larger than this one.

One the other hand, suppose you have a radiologist who is far less conservative and is willing to split them 50/50, 50 percent on this side and 50 percent on this side. Then these numbers would be equal and you would then have a gain in sensitivity, but you would lose specificity. You would end biopsying more. Well, you know, I am not sure then, of course, the device hasn't really helped.

It depends very much on that indeterminate category how many would have been put on each side of the line by each radiologist and it is possible -- I mean, I have trouble with this. But is it the case that a radiologist, who is very, very conservative will put 90 percent over on this side, shouldn't use this machine, you know, because they are going to lose in sensitivity?

I don't know how to answer this. I am just trying to clarify the question.

DR. FIELDS: Let me take a quick shot at it.

We know that about 5 percent of the cancers don't show up on mammography, no matter what you do. We know that about 5 percent of the cancers, plus or minus, we misinterpret. We know that about another 5 percent of the cancers might be there or are there because -- you can see them in -- with technical additions or better technical mammograms, you can see them.

We know we have a false negative rate on mammography of anywhere between 80 to 95 percent. There are all kinds of figures. So, in no way can 90 percent or higher be in the LOS 3 and above category. A lot of them, according to what goes on now in the clinics exist in the 1 and 2s -- in the LOS 1 and 2 in actual clinical practice.

So, I don't feel confident that the theoretical possibility that everybody goes into an LOS 3 or above could happen.

DR. HALBERG: Well, actually, it is the opposite one we worry about most is missing more cancers because of where you place the cut point.

DR. PEARLMAN: This is Dr. Pearlman.

I don't know if anyone here has had your statisticians run an analysis if you put the cut point 3 to

4, but the mammographic sensitivity drops dramatically. So, if you are worried about missing cancers, you don't want to raise the cut point. You want to lower it.

DR. BUNCHER: We were just questioned on the issue of --

DR. KOPANS: Can I just -- but don't forget all of these lesions were still biopsied because it presumed -- well, see, that is the problem. You have got clinical in there as well if you pull out the clinical and look at the mammographically protected lesions.

Sorry.

DR. BUNCHER: We were just queried on the question of what different radiologists would do. I think we have some of the answer here. While these people might have been told the same thing, they are different radiologists. They are different observers. If we look at the right hand columns, we see that they all tend to be in that category of for the negative -- the specificity improves, even though clearly they have got to be using slightly different boundaries. They are not going to be all using the same boundaries.

So, there appears to be a great robustness if you will to improving the specificity when one adds in the T-

Scan information.

I mean, I agree with the question but I think the answer actually is there. The answer is that a series of different radiologists all managed to improve their specificity without hurting their sensitivity. I mean, let's just hold sensitivity consonant -- without hurting your sensitivity, they improved specificity. That is what I think is the main claim the company is asking for.

DR. SACKS: I would agree that is what that shows here.

DR. HALBERG: And that is basically what the first question is on the discussion point that we have for review. Perhaps I can ask Mr. Monahan to put those questions up.

MR. MONAHAN: I would like to read a little bit of background, although I know most people have it.

Whereas, data from the PMA claimed to show that the TransScan device discriminates benign from malignant tissue better than chance and provides statistically significant improvement in both sensitivity and specificity in the LOS 2 and 3 category, as defined by the sponsor for the purposes of this study, the sponsor must also demonstrate that these results will translate into clinical benefit for a definable cohort of women in the U.S. and that

appropriate labeling can be written to establish with a reasonable degree of certainty the safety and effectiveness of this device.

To that end, we would like the panel to address the following issues:

1(a) Has the sponsor demonstrated that there is a group of intermediate risk patients that in clinical practice can be equated to the LOS 2-3 groups in this study in whom you would expect to see improvements in, one, sensitivity, two, specificity and, three, both?

Could I have the next overhead, please?

Does the labeling for this device adequately define the appropriate target population, as well as those women for whom the device should not be used?

Finally, has the sponsor provided an adequate training program to address not only the functional use of the device itself, but also how this device fits into and/or changes the algorithm of breast cancer diagnosis currently employed in the U.S.?

What I would like to do now is just put 1(a) up, if you would, Bob, and throw that open to panel discussion.

DR. KOPANS: I am concerned about using sensitivity data because my reading is that sensitivity was

not statistically significantly increased.

Specificity did reach significance and if our statisticians are happy with that, I would accept that. But I don't think we can say that the sensitivity, although the numbers are in the right direction, they don't reach accepted levels of significance. So, I don't think that claim can be made, based on these data.

Again, I would love to see all the -- everything redone for non-palpable lesions.

DR. HALBERG: Dr. Hackney.

DR. HACKNEY: I would have the same problem that I brought up before. When we say "in clinical practice," we are talking about a different circumstance than that was used for this study. So, at best, we could say that they demonstrated under the conditions of their study, they may have had an improvement in specificity but if conditions of their study are so different from clinical practice that I am not sure what the result would have been in clinical practice.

DR. HALBERG: Do you want to address that quickly?

DR. PEARLMAN: Could I quickly just address it?

There was one important subgroup of patients in whom both sensitivity and specificity had significant

improvement and that is women under the age of 50, if you recall the slide. We had significance on that as well.

The other point I wanted to address was, once again, yes, there is a difference between actual clinical practice. We have been saying that as loudly as you have. And I would just once again point to the study that Dr. Laver did in which of the 293 biopsied patients, only 49 had malignancies and, yet, the specificity of the T-Scan exam was 74 percent.

So, I would think that would give you an idea that in -- these were patients that were read in real life. She did this clinically. I think the evidence is there.

DR. HALBERG: Dr. Alazraki.

DR. ALAZRAKI: Yes. Two questions.

First, did you -- the LOS categorization, I would almost exclude, but were there studied women with mammographically negative cancers?

DR. PEARLMAN: There were included.

DR. ALAZRAKI: What I mean is normal mammograms.

DR. PEARLMAN: Yes, absolutely. There were 13 such patients in this --

DR. ALAZRAKI: All right. Then that answer that.

The second, on the under 50 on the chart, you had

a P value of .02 with the sensitivity increase there. How many of those would have been in the LOS 2 and 3 level?

PARTICIPANT: All the changes are in 2s and 3s.

PARTICIPANT: How many in 2 and how many in 3 is what she is asking.

PARTICIPANT: I don't have that.

DR. ALAZRAKI: So, you don't have --

DR. PEARLMAN: We don't have it right now, but it is something we could get quickly.

DR. KOPANS: Again, to add to that, though, for sensitivity and -- first of all, I hate breaking women 50 and over and 49 and younger. I think that is misleading. But, anyhow, I would like to also see, you know, what percentage of the ones that were not mammographically visible were palpable. I assume they all were and then the question comes up if you eliminate the palpable lesions, do you still find cancers with T-Scan that were missed on the mammogram and what percentage?

And then the question would be why were they missed on the mammogram?

DR. PEARLMAN: There is, obviously, another negative factor that works against any new modality that is not approved for use and that is that you could not use the

modality's findings to guide a biopsy itself. So, those cases in which the T-Scan would have found something, you don't know. So, that remains for the future as we know --

DR. KOPANS: So that presumably all the cancers that were LOS 1 were palpable cancers? Or LOS 2, for that matter, I guess.

DR. PEARLMAN: We can check that, but --

DR. KOPANS: Again, I think that is important --

DR. PEARLMAN: -- predominantly, I would imagine that is true.

DR. HACKNEY: You could use follow-up to get some idea of what happens in those T-Scan positive mammo and mammo and clinical negative cases. That would at least give you an idea --

DR. HALBERG: That would be a suggestion that we can make.

DR. HACKNEY: -- which ones you are picking -- what it is that you are picking up with that.

DR. SACKS: I think you can assume that the LOS 1s were palpable because there would have been no other reason to send them to biopsy, but you can't assume that about the 2s because there are other reasons besides palpability when you see a lesion to recommend biopsy, such as strong family

history and so on.

DR. HACKNEY: We can assume that the biopsied LOS 1s were palpable. The non-biopsied and the screening tests that are also LOS 1s, we don't know what they were.

DR. BUNCHER: I would point out to you that the 1 is a re-read. It is not the original reading. It is not the clinical reading. So, the clinical reading could have been a 3 for all we know and they could have sent it on. We don't know that it is a 1. We have to consider the possibility that the re-read is --

DR. HALBERG: We are actually asked to answer this question from the FDA. Has the sponsor demonstrated that there is a group of intermediate risk patients that in clinical practice can be equated to LOS 2-3 groups in this study in whom we would expect to see improvements in sensitivity, specificity or both?

Perhaps what we should do is go around the table at this point and -- or perhaps just start with the people who are most involved in mammography.

Dr. Kopans.

DR. KOPANS: Well, again, I still have trouble with the fact that as Dr. Hackney is pointing out, in clinical practice, I think, it would be hard to say because

this was not designed to mirror clinical practice. So, I don't think you can -- certainly, the sensitivity you would have to specify that it was for only women under 50, but I still would have major problems with that because a clinical breast exam is a real phenomenon. The women were referred because of palpable masses.

So, you would have to say in women who don't have clinical breast examinations, T-Scan may add, but I think if these are the same lesions, the ones that are missed on mammography, are palpable and would go on to biopsy because they are palpable, I don't know that T-Scan made the contribution. So, it is a tough -- I don't know how to answer the question.

DR. HALBERG: Is there additional information that you would like to ask of the company?

DR. KOPANS: Again, I think, if I could see the data for non-palpables, at least that eliminates the clinical aspect of it. It doesn't answer the magnification, imaging and so on, but it would get you closer to knowing how things varied within a finite group.

I would also like to see that broken down by age as well because I suspect younger women will have more palpable cancers that are not seen by mammography, not just

at 50, but just general decreasing -- or increasing with decreasing edge.

DR. HALBERG: So, we can ask for that particular piece of information, that we get the breakdown of patients who had non-palpable lesions and that number be again broken down to those that are 50 and younger or younger than 50, however you want to make the cutoff, and those that are above that age.

DR. KOPANS: And the LOS scores --

DR. HALBERG: And the LOS scores and the changes. Let's move on to 1(b).

DR. KOPANS: Did other people want to --

DR. HALBERG: Oh, actually, is everybody in agreement with that? I apologize.

DR. DESTOUET: The only additional information I would like would be size of lesion and depth of lesion in the breast.

DR. HALBERG: Can you provide depth?

DR. PEARLMAN: No. Depth of lesion was not a measure that was in the study.

DR. DESTOUET: Even on the mammogram, you don't know --

DR. PEARLMAN: It wasn't a measure that was part

of the study.

DR. DESTOUET: I see. When you look at the BI-RADS, there is, indeed, a way to indicate the depth of lesion in the breast but that is not something you looked at?

DR. PEARLMAN: It wasn't part of the design of the study. It was not entered into the database --

DR. DESTOUET: I think, given the comments of Dr. Smathers, that you don't have a phantom with which to zero in this machine, you really don't have an analysis then of the depth of lesions that this technique can detect.

DR. PEARLMAN: We are developing a phantom to do this. And we believe that we will have something within the coming months. In the meantime, again, I want to emphasize that the device is an impedance measuring device, the images formed from impedance measurements. Each and every sensor in the device is calibrated against a standard every time you use it.

DR. KOPANS: Can we get sizes? I didn't want to let that slip away -- get sizes as well. If you could make it clear, you have got sizes in the PMA for tumors but it looks like you have got the sensitivity presumably are the cancers and the specificity presumably are the benign

tumors.

DR. PEARLMAN: Yes. If you would like, we have a scattergram of size and age to show the comparison.

DR. KOPANS: Size and age?

DR. PEARLMAN: Yes.

DR. GATSONIS: There are other issues that could be analyzed further. I didn't understand that we had that option at this point. I thought at this point we were asked up or down on this recommendation. Because, I mean, there is one issue that we haven't discussed at all. Why did the company choose to have the TransScan be interpreted as a plus 1 or minus 1? Why not plus 2? If the TransScan gives you very strong information, add 2 or subtract 2 and so on. I mean, there is -- the rule -- I mean, part of why we are dealing -- we are stuck in the 2, 3, 3, 2, is exactly, you know, an artifact of the fact that you were allowed to add only 1. I didn't understand the rationale for that.

I suppose there is a rationale.

DR. BUNCHER: The only rationale is that it was pre-chosen and we did nothing to optimize the method of changing the score. All of that was pre-chosen prior to the trial and that was the attempt to have a valid scientific study where you say ahead of time what you are going to do

and then do it, but we have not yet gone to the route of how much could we improve it if we used a different algorithm.

DR. GATSONIS: Yes. I mean, presumably what you would see is TransScan will give you a very strong scan versus a not so strong scan. Then you would weigh differently. You wouldn't just add one. You would add two or you would add nothing for that matter.

It is sort of a -- it is a rule that it was not -- that doesn't -- is not germane in my mind. So, if you are going to think about how you optimize this, you have got to optimize it and look at various options.

DR. PEARLMAN: I have to agree with that comment. In fact, we believe that we may be able to do even better in the future, but we had to start with something and we got the investigators to agree on this simple rule, which was understandable. It is certainly a reasonable place to start. It is by no means the last word, but the point is even with this modest beginning, the results speak.

DR. HALBERG: I am going to just ask that the manufacturer and Dr. Sacks just move away from the table and that we limit the discussion to just the panel members and then ask you to respond to specific questions, if that is okay. I think that might move this along a little bit

faster.

So, what I am hearing is that we are asking the manufacturer for more information.

Dr. Kopans, do you want to summarize what that additional information would be for us?

DR. KOPANS: Let's see if I can remember now.

I think we would like to see size data and particularly for cancers and particularly for the non-palpable lesions, the various breakdowns of LOS and how they change with TransScan again for non-palpable lesions, also by age.

DR. HALBERG: Are you okay with that?

DR. ALAZRAKI: Yes. And also in -- well, you said by age, but the under 50 year group was --

DR. HALBERG: Right. Specifically, the younger women.

DR. ALAZRAKI: Right.

DR. HALBERG: Okay. On to 1(b).

Does the labeling for this device adequately define the appropriate target population, as well as those women for whom the device should not be used? Let's concentrate on the second half of that sentence, the group of women for whom the device should not be used. Are there

specifically women that we can identify in that category?

DR. KOPANS: Again, I think the labeling needs to be very specific and I am not sure how to do that because this was a specific group for which there is a -- there looks to be a benefit and that needs to be carefully defined. You wouldn't want someone misunderstanding and taking a spiculated lesion, having a negative TransScan and saying she doesn't need to be biopsied. So, the labeling is going to have to be very, very tightly written.

DR. HALBERG: And, Dr. Sacks, the FDA can address those labeling issues.

Let's go on to 1(c). Actually, I apologize. Do other panel members -- Dr. Alazraki.

DR. ALAZRAKI: Yes. I think, well, clearly, we are talking about women who by all other conventional modality examination, mammography certainly having been done before and there are other imaging modalities, which have higher, you know, sensitivities and specificities than what we are looking at here. I would think that they would be done first before going to the T-Scan.

So, I think what we want to say here is that we would recommend that it not be used for women who otherwise would be sent for biopsy.

DR. DESTOUET: I am actually not sure what the answer to 1(b) is. I think there probably is a very small subset of women, who following all the conventional means we have now to evaluate those women, are left in that nebulous category of I don't know what to do with them. I don't think the manufacturer has really identified that subset of women. I think we need more data.

DR. KOPANS: The manufacturer, I think, also says it can differentiate benign from malignant and I would be very, very careful in not allowing that. I don't think the system has been shown to differentiate benign from malignant.

DR. GATSONIS: I think the only agreement that I sense around here is those who should not perhaps be is those in category 1 and in category 5. Anything else in between I don't see that it has been proved that T-Scan helps or doesn't help very much. Just to continue on this point, if we make any choice in this 1(b) that goes beyond the 2 and 3 category, then we will have to reanalyze the data, as if those were the women on which TransScan was being evaluated and then we will come into some of the issues that were discussed in the FDA presentation.

DR. ALAZRAKI: If we look just at the LOS 2 and 3,

what we don't want to do is see a new tool come along, which is going to put women who otherwise would have gone to biopsy, who may have had a cancer, fall into a category of you don't have to go to biopsy and miss the cancer. That we don't want to see.

It is okay to see it go the other way. It is okay to see women who either may not go to biopsy, who this test says, yes, you should send this woman to a biopsy, that is okay. We will pick up a few cancers, which otherwise would not have gone to biopsy. But the other way, we don't want that to happen. So, I think you have to say that this is not an appropriate test for women who by other conventional -- first of all, the screen and mammography is still the only screen -- by other conventional methods are scheduled for or are thought to need a biopsy, those women are not appropriate for study with this.

DR. GATSONIS: That assumes that if you tell a woman that there is suspicion and you send her for biopsy, that doesn't send her in a tailspin somehow and there is no major curse with that, as well. I mean, in a sense, you are making an implicit judgment there. I probably share your judgment, but I think it should be made explicit in any discussion like this.

DR. HALBERG: Dr. Romilly-Harper, Dr. Destouet, Dr. Kopans, do you want to comment on that, essentially not looking at the specificity data? That is what you are saying basically.

DR. ALAZRAKI: Yes, because the sensitivity data isn't good enough to warrant that, I think. I mean, it is just not strong enough.

DR. DESTOUET: You have to look at the specificity data. You can't either send everyone to biopsy or no one to biopsy or just --

DR. ALAZRAKI: We are looking only at the LOS 2 and 3 group.

DR. DESTOUET: So, you still have to look at the specificity data.

DR. KOPANS: It seems to me it is very -- you have got to get from the company and the radiologists precise definitions of what LOS 2 and LOS 3 were and it is only for those categories that you have shown statistically significant specificity improvement and the sensitivity is still, I think, up in the air. Well, I think they are both up in the air because of the palpable issue because that -- if you have three different parameters, there should have been different assessments, including the clinical breast

exam.

So, again, this may all change with the non-palpable lesions, but you still have to really define what the lesions were that fit into LOS 2 and 3.

PARTICIPANT: I agree with that. You need the specificity.

DR. HALBERG: Is that enough clarification for 1(b)? Okay. On to 1(c). Has the sponsor provided an adequate training program to address not only the functional use of the device itself but also how this device fits into and/or changes the algorithm of breast cancer diagnosis currently employed in the U.S.?

DR. KOPANS: And I apologize if I don't really fully know the training program and I am sure I don't.

I think the atlas, if that is part of the training program, I would say has major weaknesses. The mammograms are only single view mammography. They are very hard to even look at and see what is being pointed to. So, if that is the level, there needs to be a major improvement.

I suspect there is more that the company is doing than that. But I think that needs -- I am not aware of it. That is the thing. I think we -- in order to say anything, I would like to hear more about the training.

DR. DESTOUET: I think even asking Dr. Fields how this fits into his algorithm for evaluation of the either asymptomatic or symptomatic patient, I am still unclear as to how these women logically progressed from screening mammography, additional views, ultrasound, T-Scan. What is the impact of each of those studies in the analysis and/or decision-making process? So, I think we still don't have enough --

DR. HALBERG: So, we would like to ask the manufacturer for a very rigorous algorithm for how they would use the TransScan information. Is that what I am hearing?

DR. ALAZRAKI: But it has to be supported by data.

DR. DESTOUET: Either long term follow-up or biopsy would be the data.

DR. HALBERG: So, we are asking for additional information and the data to support it. Okay.

Mr. Monahan, would you like to read the preamble to Question 2?

MR. MONAHAN: Yes. Let me do that.

A concern is raised by the fact that the adjunctive combining rule used by the company in the trials was to adjust the mammographic level of suspicion, LOS, by

adding or subtracting 1, or leaving it unchanged, depending on the T-Scan result. This rule is dependent on the radiologist's use of the company's LOS scale which differs from the ACT BI-RADS scale, which leading mammographers seek to make the standard mammographic lexicon in the United States. Specifically, the BI-RADS 4 category corresponds to the TransScan LOS 3 and 4, as presented in this PMA.

This discrepancy gains additional significance given that the ROC analysis of the PMA data set for the adjunctive use of mammography/T-Scan only shows a positive additive effect over that part of the ROC curve for the lower suspicion lesions and, in fact, dips below the ROC curve for mammography alone at the higher suspicion region of the scale.

For example, were a radiologist to apply the T-Scan to a woman in TransScan LOS 4, who would, in the absence of the device, be recommended for biopsy, and the device gave a negative result, the instruction to the radiologist would be to subtract 1 from the TransScan LOS, with the result being 3. By the definition of the TransScan scale, this 3 would not change the recommendation for biopsy. However, should the radiologist instead subtract 1 from the BI-RADS 4, the resulting BI-RADS 3 would dictate a

recommendation of six month follow-up, rather than biopsy. In the clinical trials approximately 25 percent of the women with cancer in this category would, therefore, be denied the immediate biopsy.

If I could have the question itself?

Has the sponsor adequately addressed the need to bridge the gap between the radiology community's growing use of the ACR BI-RADS scale and the need for them to use a finer division within the ACR 4 category when using the T-Scan, in order to avoid postponing diagnosis in a sizable group of women? If not, please suggest additional instructions for use to be incorporated in the labeling of this device to resolve any confusion between the two rating scales and thereby enable radiologists to use the device safely and effectively. In particular, should the labeling include instructions to the radiologist to use the TransScan LOS scale as well as the adjunctive scoring rule employed in the PMA when interpreting results of the TransScan test?

Could I have the next transparency, please?

And, finally, 2(b), is the training program recommended by the sponsor adequate to address this issue? If not, what kind of training do you think would be appropriate?

If we could go back to 2(a), Bob, and open that up for discussion.

DR. KOPANS: I think, again, this goes to the definition of LOS 2 and 3. I agree, I think there is going to be confusion because we have been working so hard to get the ACR scale used to now have similar numbers, will be confusing and will be misunderstood. We could perhaps change it to A, B -- you know, the TransScan A, B, C and D or something like that. But, again, you have got to define what 2 and 3 are or B and C, however you are going to do it, so that radiologists would get away from BI-RADS for this particular analysis and understand what it is they are doing.

DR. HALBERG: Dr. Destouet, Dr. Romilly-Harper.

DR. DESTOUET: I think if you had a subset of cases where you could have a training film set to allow your participating radiologist to learn from, a learning set, where you could, indeed, categorize those according to the BI-RADS category, I would like to see it stay within the BI-RADS category because that we are all familiar with.

Not only can we get the level of suspicion data, but we could also get other data, such as depth of lesion, location of lesion, that sort of thing. I think, perhaps,

you could decrease the inter-observer variability and, perhaps, kind of train your radiologists what is LOS 1, what is LOS 2 and further on.

I think otherwise you will have a replication of this kind of indecisive categorization of lesions.

DR. ROMILLY-HARPER: I concur with Judy because I really think I would like to see it go back to the ACR BI-RADS for the training set and I think it will decrease significantly the re-reading error rate.

DR. GATSONIS: Is the zero category in the BI-RADS something that should be of concern here? Should we be discussing that? Because, obviously, that category is a thorn in the side of anybody who wants the diagnostic test. It is a nonsensical category that is there to keep people out, but when you evaluate a diagnostic test, to put a bias over, but when you try to evaluate a diagnostic test, you cannot have that as a category as if it is a diagnostic test.

DR. KOPANS: Just quickly, category 0 in BI-RADS needs additional evaluation and that is only a temporary category. No one should have that as a permanent diagnosis or assessment. The problem, as Dr. Hackney was saying, is that -- well, probably about, in our practice, 6 percent of

screening women go into that category and have to get additional views and then we make a final assessment and that is lacking, of course, because of the study design and it is a problem.

I mean, you know, I think that the fact now that breast imaging is a multi-level assessment, where does TransScan fit into that? That was the question asked earlier. But I think that -- I think BI-RADS is what everyone is now familiar with. The problem is that this LOS score on which the statistics are based on broke BI-RADS 4 into two categories. If you are going to do that, then you have got to define the lesions that go in LOS 2 and the lesions that go in LOS 3. But that is the only way it will work, I think.

DR. ALAZRAKI: I just -- I am not a mammographer, so I don't do this everyday and I don't use those scales, but it seems to me -- and I would yield to the mammographers here, but it seems to me that there is not a one-to-one relationship between this LOS and the BI-RADS and that the level of confusion is going to be escalated by trying to match them and that instead of trying to do that, that it makes more sense to me to talk in terms of what the LOS talked in terms of and that is whether or not there is a

recommendation for biopsy or whether or not there is uncertainty about whether or not the woman should go to biopsy.

And I still feel that this whole modality is not suited for those who would have the recommendation by other modalities to go to biopsy.

DR. HALBERG: So, what I am hearing is that everybody believes that we should still keep the BI-RADS classification and that we should further define within the BI-RADS classification what subgroups of women this is appropriate for. Does that sort of summarize what we have said?

Okay. With that, let's go on to 2(b). Is the training program recommended by the sponsor adequate to address this issue? And I think that I can probably already answer that we are going to want to see a training program that addresses what the categories are, you know, based on BI-RADS.

DR. KOPANS: I think, again, I think the radiologists would all agree -- I want to know what kind of lesions were LOS 2 and LOS 3. In order to use this the people who are going to be using it have to be trained in those lesions. That is the only way I can see it having any

efficacy.

DR. HALBERG: I think the efficacy has to be on a good training program that everybody can understand.

MR. MONAHAN: Again, I will read the introductory remarks and then we will put up the actual questions for the final question for the panel to consider.

As with other diagnostic modalities, there appears to be a subset of women with malignant lesions in whom the device failed to detect their cancers and women with benign lesions in whom the device suggests malignancy. With a mammography, the presence of very dense breasts and certain tissue types are known to reduce the reliability of the examination. It is not known what characteristics of lesions or surrounding breast tissue lead to device errors for TransScan. The PMA data suggest that lesion size and depth are not the explanation, but there are no data relating histological characteristics to device error. There may also be other explanations to account for some of these errors and I believe we have discussed some of them today.

Bob, if I could have 3(a), please.

Should the sponsor be required to provide data necessary to identify these women, so that the labeling can

identify them as patients at higher risk for a false negative or false positive readings?

And 3(b), if so, must we have these data prior to approval, or could the sponsor provide a methodology for accruing such data postmarket?

If we go back to 3(a) and open that up for discussion.

DR. KOPANS: Again, along with characterizing LOS 2 and LOS 3 lesions, you know, I think it would be -- do we have any data suggesting what type of women were missed on mammography and had their cancers detected or moved to LOS 3 with TransScan or do you have breast tissue density patterns in the database and so on?

DR. PEARLMAN: This is Dr. Pearlman.

It was noted if the breast was dense. However, the numbers you are talking about are small. As you can see, there are only 16 wins. You are not going to do a lot of statistics on 16. This is certainly a worthy topic for further study.

DR. DESTOUET: I think, clearly, if you look at the pilot study of Dr. Laver-Moskowitz, that there is a subset of women in whom there is a higher false positive reading and it may be those hormonally responsive women,

women who are either premenstrual -- she actually recommended a time interval where these women should not be evaluated.

I think, clearly, before we implement this type of study, we need to know which women are expected to have a higher false positive rate. I think Dr. Fields said he was looking at some of those women who are either on hormones or actually premenstrual, that sort of thing. So, there clearly is more data we need to know.

DR. GATSONIS: Frankly, I think that is something that they should be doing after an approval or disapproval. I can't see the manufacturer responsible for data like this. I mean they are too detailed.

DR. DESTOUET: Well, I tend to disagree. If part of what the manufacturer is saying that this test is efficacious in the dense breast, women under age 50, it may be that that is the very subset of women who may have false positive T-Scans because they are ovulating.

DR. GATSONIS: I agree. If it is a matter of labeling, we should take this out of labeling, but really to get into that kind of subset population up front --

DR. DESTOUET: I don't know.

DR. HALBERG: Is that enough feedback then for you

on terms of 3(a)?

DR. ALAZRAKI: I would think that the women with dense breasts, who often -- not often, but sometimes have mammographically difficult to interpret studies would be a group that physicians might tend to want to use this in and I don't think we have the data, you know, in that group to support allowing that type of use.

So, I would think that we would want the company to give us that data if they want that to be included. If they don't, then we should exclude that in the labeling, that group.

DR. HALBERG: Let's go around the table maybe and get everybody's feeling. Shall we ask the manufacturer for more data on younger women, dense breasted women in terms of --

DR. KOPANS: First of all, dense breasts don't necessarily mean younger women. There are a lot of older women with dense breasts. I would like more data. I don't know -- I am going to pass. I don't know what to say on this.

DR. ALAZRAKI: If you pass, I don't know how I can --

DR. KOPANS: I am just concerned that I don't know

what the population is that this technology benefits. I just don't have enough information to know how to advise the company as to labeling or the FDA as to efficacy. I mean, there is an improvement in specificity and maybe an improvement in sensitivity in younger women, but I don't know for what lesions. You know, LOS 2 and 3 have no meaning for me at this point and I don't know what -- you know, I don't think you can say it is for any particular type of woman because those data weren't presented and I am sure it is going to be hard to get at.

It would be all women in LOS 2, LOS 3, I presume.

DR. HALBERG: Did you want to make a comment?

DR. GATSONIS: No. I mean, I just don't -- I don't think it is necessary to ask this at this point and it should not be labeled for that. The labeling should not include that kind of special -- I mean, here it is sort of Phase 1 and we are asking Phase 3.

DR. HALBERG: Dr. Romilly-Harper.

DR. ROMILLY-HARPER: I am just having a hard time, like Dan is, determining what population is best to utilize the equipment on. I just think there is not enough data of any category, whether it is dense breast or not. I agree, when we get to that point, I think, we need -- we would need

some type of evaluation as to which patients are at high risk for false negatives and positives, but I don't think we have the information.

DR. HALBERG: Dr. Hackney.

DR. HACKNEY: I think the manufacturer has given us the data that they have and I can't imagine what size study would be required for them to identify enough false negatives and false positives to then subcategorize those and identify patterns of which women and which sorts of breasts would be most likely to have these problems.

So, I think if we ask them to provide that before this is approvable, it could be a very long time before it could even come back. I have made it clear before that I am not that comfortable that the data we have let's one translate their study into clinical practice and I don't see how they could comply with this with the information they have or that they accumulate in any reasonable period of time.

It took a long time to figure out what was wrong with mammography in the areas where you have problems. You are essentially asking them to do the same thing for this technique.

DR. HALBERG: I think basically the people's

comments around the panel have also addressed 3(b). You may want to put 3(b) up. I am not sure we need to have a lot more discussion about it in light of the discussion we have just had. I think we are asking for more data.

Would you like to respond to the sets of issues that have come up?

DR. PEARLMAN: Yes. Thank you very much. This is Dr. Pearlman from TransScan. There have been a number of very important comments made that I would like to respond to.

With regard to postmarket study, as I have indicated, the company already has active plans that we are pursuing to investigate the issues raised in points 3(a) and (b) because they are interesting to us, as well as to the medical community. We believe that not only is it interesting and important to understand in what patients this may be better indicated than others, but also can we sharpen up the technique and make it more effective.

So, we are interested in this, as you are. What I would like to point out is the issue of providing a warning as to whether there is a type of patient that is less likely to be benefited by this technique than others. Other than the guidelines that we have suggested, such as ruling out

patients that are clearly indicated for biopsy, such as Dr. Alazraki has suggested, that is clearly contraindicated and it is in our labeling that we are recommending or clearly ruling out patients that are clearly indicated for follow-up. That is also in our indications ruled out.

Other than that, we do not know from our study any single factor, whether it be the age, the breast size, the size of the lesion or the menstrual status of the patient that shows a statistically significant impact on the adjunctive rate. It all appears to work. So, we don't know of a warning sign right now that we could tell you for the next woman walking in. We usually watch out because we are suspicious that we will not be accurately diagnose you. There are no such indications that we know of right now.

Although it was mentioned that we are investigating -- it is interesting to look at the menstrual cycle. We don't have a rule for that and any clear message from that that we could say to you right now that these women or the other women are not indicated for this test.

So, therefore, I would like to appeal to the reason that Dr. Gatsonis, that these things are interesting to us as well as to you. We would hope that the fact that we did a very strict study design, as Dr. Kopans has pointed

out, would not be used against us in estimating what this can do in the actual clinical utility. Had we wanted to do a study that was more clinical in nature then the criticism would have been the other way around, that you don't know who is helping what and you have a big mess.

So, we thought we were doing the right now by going the blinded route and we would like not to be penalized for that. Thank you very much.

I would also like to invite Dr. Fields and Dr. Rossmann to address the issue of the right patients, as we understand them, for the study. We have, as Dr. Fields presented earlier, a chart that illustrates conceptually how this fits in and for whom it is indicated. Would that be appropriate at this time?

DR. HALBERG: If it can be very brief.

DR. DESTOUET: Dr. Halberg, I do not want this to sound that nebulous, but I think there are women who are put on hormonal replacement therapy for whom we had no data and there is not question that some of these women would be included in this study. Would such a therapy change their T-Scan? I am sure that doesn't have to be accumulated prior to premarket approval, but I think that there are probably some women and even as was pointed out in their pilot study,

some women who are premenopausal may have false positive T-Scans suggesting that there is a hormonal effect. So, I would like to know if, indeed, that is valid.

DR. HALBERG: So, in response to that, one of the things we would also like to ask the manufacturer for is more data with respect to hormonal status, either menopause or hormone replacement.

DR. FIELDS: I just want to refer again to my flow sheets here. In my current practice, I don't define LOS 1s, 2s or 3s. I don't examine patients that are definitely benign or I have decided should have follow-up or should have biopsy. It is only those indeterminate cases based on all clinical information. I have defined anything here, any category, other than the fact that it is an indeterminate case. They might have indeterminate microcalcifications, which we see everyday; equivocal masses we see everyday, other things.

Mammographically, they might be indeterminate for other reasons as well but I have decided on clinical grounds that this is an indeterminate case, probably benign by its nature and the T-Scan tries to help me with that.

DR. KOPANS: Again, just to reiterate -- I appreciate the flow chart, but, for example, I don't know

what indeterminate microcalcifications are. Equivocal masses, do you do an ultrasound and show their cysts or does this eliminate cysts. These are equivocal solid masses.

DR. FIELDS: Equivocal solid masses, right.

DR. KOPANS: And are those masses where you think there is an obscured -- I mean, I could -- this is where I think you need the detail. What did the re-readers specifically categorize as LOS 2 and LOS 3? Because that is where your theoretical efficacy is and that is only where it is, unless I am missing something. As an experienced radiologist and breast imager, I need to know really what were the criteria being used for these grades because otherwise it is a huge waste basket and there are going to be -- someone is going to say, well, you know, it has got a little defined margin. That must fit into the T-Scan, when, in fact, it is actually an invasive cancer that has an ill-defined margin.

So, I think it needs to be more specific so I know what the indications are for using the scan properly. You may have the gestalt. I have no doubt you do because you have used it, but someone coming along has to have specific indications, I think, for when to use it and what are the specific lesions that the study showed as opposed to what

your -- I mean, we all incorporate our own experience and we need to have the objective analysis.

DR. ROSSMANN: I think that that is a very fruitful suggestion and I think that that is something we could do.

DR. HALBERG: Thank you.

Let me now -- let's proceed with the review and discussion of this PMA P970033. Mr. Monahan will remind us of our responsibilities in reviewing this PMA.

MR. MONAHAN: I would like to note for the record that in the conflict of interest statement that I read this morning, there was an omission and the omission was that Dr. Griem could participate in the discussion for TransScan. However, he was prevented from voting because of a potential conflict of interest or the appearance of such.

The point is moot because he had to catch a plane. So, he is not here, but I felt that it was necessary to let you know that.

We are asking -- and this will be redundant with this morning's explanation, but I would again like to read the instructions to the panel into the record for their -- concerning their recommendations.

We are asking them to make a recommendation as to

whether this PMA should be found approvable, approvable with conditions or not approvable. There are three options. A recommendation must be supported by data in the application or by publicly available information. Your recommendation may take one of three forms.

You can recommend that the PMA be approved with no conditions attached to the approval. You can recommend that the PMA be found approvable subject to specific conditions, such as resolution of clearly identified deficiencies, which have been cited by either yourselves or by FDA staff. Examples can include resolution of questions concerning some of the data or changes in the draft labeling.

You may conclude that post approval requirements should be imposed as a condition of approval. These conditions may include a continuing evaluation of the device and submission of periodic reports. If you believe such requirements are necessary, your recommendation must address the following points: (a) the reason or purpose of the requirements; (b) the number of patients to be evaluated and (c) the reports required to be submitted.

You may also find the application not approvable. The Act, Section 515(b)(2) A through E states that a PMA can be denied approval for any of five reasons. I will remind

you of three of these reasons that are applicable to your decision.

The three are: There is a lack of showing of reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the labeling. To clarify the definition of safe, there is a reasonable assurance that a device is safe when it can be termed based on valid scientific evidence that the probable benefits to health from use of the device for its intended uses and conditions of use when accompanied by adequate directions and warnings against unsafe use outweigh the probable risks.

The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.

The PMA may be denied approval if there is lack of showing of reasonable assurance that the device is effective under the conditions of use prescribed, recommended or suggested in the labeling. A definition of "effectiveness" is as follows: There is a reasonable assurance that a device is effective when it can be determined based upon

valid scientific evidence that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use will provide clinically significant results.

And, thirdly, the PMA may be denied approval if based on a fair evaluation of all the material facts the proposed labeling is false or misleading. If you should make a non-approvable recommendation for any of the stated reasons, we request that you identify the measures that you believe are necessary or steps which should be undertaken to place the application in an approvable form and these may include further research.

I will turn the meeting back over to Dr. Halberg.

DR. HALBERG: If there are no further items that the panel wishes to discuss, we will move to the panel's recommendations concerning the PMA P970033, together with the reasons for the recommendations as required by Section 515(c)(2) of the Act. The underlying data supporting the recommendation consists of the information and data set forth in the application itself, the written summaries prepared by the FDA staff, the presentations made to the panel, which we heard today, and the discussions held during

the panel meeting, which are set forth in the transcript.

The recommendation of the panel will be approval, approval with conditions that are to be met by the applicant or denial of approval.

Can I get a motion?

DR. ROMILLY-HARPER: So moved.

DR. HARDING: Do you want to move for approval, approval with conditions or denial of approval?

DR. ROMILLY-HARPER: Are we going to go around or --

DR. HARDING: Actually, I first need a motion.

DR. ROMILLY-HARPER: Repeat those three categories again.

DR. HALBERG: Approval, approval with conditions or non-approval, denial of approval.

DR. ROMILLY-HARPER: I vote for non-approval at this time with conditions because of the following: I have problems with the data that was presented. I would like to see improvement in consistency of the physician interpretation of the mammographic data.

I think this application of the differences in capacitance and resistance of tissues is excellent. I think the company has done a tremendous job. I think the

information, however, that we received today and the information that was presented to us, both by the company and by the FDA leaves a lot of doubt in my mind as to how to exactly proceed on an approved status.

DR. HALBERG: So, the motion on the table is for denial of approval with a request for additional information as we have outlined in response to the three questions that the FDA put before us.

Is that a fair summary?

DR. ROMILLY-HARPER: Yes, it is.

DR. HALBERG: Do I have a second?

DR. HACKNEY: Second.

DR. HALBERG: Could I have a show of hands for people agreeing with the motion?

Can I poll everybody on their reasons? Perhaps I will start with --

MR. MONAHAN: Excuse me. For the record, could you count the number of votes, please?

DR. HALBERG: For the record, one, two, three, four, five, six -- all of the -- are you abstaining?

DR. ALAZRAKI: Yes, I am abstaining.

DR. HALBERG: For the record, there were five votes for the motion and one abstention.

Now, Dr. Hackney, we will go around the panel and poll you for your reasons for your vote.

DR. HACKNEY: I think there was a lack of evidence of effectiveness as it is intended to be used in clinical practice and for that reason I am not convinced that it is safe since it may lead to some women not undergoing biopsy, who might have undergone biopsy otherwise and it is not clear whether there will be a larger increase in needed biopsies being performed as a result of this than the decrease in needed biopsies not being performed.

And I think that that question could be answered by a study that fitted this T-Scan data into clinical practice. So, at this time, I don't think there is enough information to conclude that it is either safe or effective.

DR. DESTOUET: I am not sure in whom I would use modality and, as someone who reads about 25,000 mammograms a year, I need more data regarding which patient population this study -- this test is best suited for and I need to know how this will affect management of those patients.

DR. ROMILLY-HARPER: I just want to comment to the manufacturers, I really think that this is a technology that needs to be pursued and not let it drop because I think we all would like to see an adjunct to the current status of

detection of breast cancer.

However, I would like to see according to the discussion today a lot of tightening up, not necessarily massive numbers, but tightening up of the data that is available and a pursuance of some more critical aspects of obtaining that data, particularly that LOS 2-3 category because, as Dr. Destouet says, as clinicians we are having a problem determining how effective this is going to be in solving the problems that they really want in the breast. When should we use it? In whom is it going to be beneficial? And particularly, are we going to increase the number of biopsies on patients that don't need them?

Those things, I think, we addressed today and I think can be answered, whether it takes a few months or what have you, but I think it is doable.

DR. HALBERG: Dr. Gatsonis.

DR. GATSONIS: Yes. I mean, this is a very difficult vote for me in the sense that I think these sponsors did -- I mean, tried to play by the rules, the new rules of providing substantial evidence, designed studies and making technology evaluation a serious scientific field.

The down side of that is often there are too many loose ends that show up in this kind of application. That

is what it showed up. This is why my vote is such. I think that with the information that was -- we said should be provided in all the previous questions of the FDA, if this was on the table, I would take another very hard look at this and my answer might be different.

DR. HARDING: Dr. Alazraki.

DR. ALAZRAKI: Yes. I abstained. I think that the conclusion here is reasonable. The reason that I abstained is that I felt I could also have gone the other way, a very limited, very highly conditioned approval at this point. However, I think that the company can, based on discussions that we have had now today, perhaps gather some more of that specific population targeted data that I think the committee felt it needed and come back and perhaps that would just -- also, the data presented by the FDA was new to me and I think it was a little bit difficult to digest everything in two or three hours.

DR. KOPANS: I think I would basically second what everyone has said. Again, I give the company enormous credit for doing the study the way they did. Again, I think there were unfortunately some major loose ends, but I would encourage the FDA to work with the company to tie up as many

of those as possible.

Again, it is almost unfortunate that you have to kind of make a vote because I am not sure -- to me, it is just we are not quite there. I do have concern -- I think those of us who are involved in breast cancer detection and diagnosis see women everyday where cancers are missed. I think we would probably all agree that is one of the most devastating things that we all face.

I just don't want to approve something where conceivably that could -- that number could increase. Now, at the same time, it may be that the system is going to decrease that. I think the level of the information that I have at this point doesn't allow me to comfortably say that. The data may be there and I certainly would love to see them and look at it some more, but right now, I would not be comfortable in recommending approval, but I think certainly getting at the data and looking at it some more, I would strongly encourage FDA do that.

DR. HALBERG: Ms. Whelan, do you want to make any comments?

MS. WHELAN: Not really. The only thing I would say is that not being a mammographer or a statistician, this is mildly overwhelming to listen to all the discussion in

the review, but it occurred to me that as a consumer, it would be quite difficult to participate with your health care provider in making a decision about the use of this technology if it is not made to the clear to the clinician what an LOS 2 or 3 is.

DR. HALBERG: Thank you.

I want to thank all the members of the panel for their hard work in reviewing this and their fortitude in remaining here and for the recommendations to the FDA concerning SoundScan 2000.

Since there is no further business, I would like to turn it over to Mr. Monahan for some closing remarks.

MR. MONAHAN: Dr. Yin.

DR. YIN: I would like to have some closing remark. First of all, I do want to thank Dr. Halberg. This is her last meeting as a chairperson, but not as a consultant, and it is a very difficult one. I really appreciate you all taking the time, give everybody the time to work this out. And thank you so much.

I want to thank the panel for a very good discussion and I do want to thank the sponsor also. You have heard all our experts here tell you that, indeed, this product is reasonably useful. So, if you can come back with

all the data and, hopefully, that we will not change our minds. Whatever we ask you, we expect that it will go through the next time, we hope.

Thank you so much from all of you.

MR. MONAHAN: I would like to just note before we leave that this will be my last meeting as exec sec and I would like to thank the panel, all the members for making my job easier over the last few years as we went through these various meetings. I am going to miss you but I am sure you will see me around. So, thank you again and I think this meeting is adjourned.

[Whereupon, at 5:22 p.m., the meeting was concluded.]