SUMMARY MINUTES

SEVENTY-SECOND MEETING OF THE OBSTETRICS AND GYNECOLOGY DEVICES

ADVISORY PANEL

MEETING

August 29, 2006

Hilton Washington D.C. North
Gaithersburg, Maryland

Attendees

Chairperson (Acting)
Marcelle Cedars, M.D.
University of California
San Francisco, CA

Voting Members

Paula Hillard, M.D.
University of Cincinnati College of Medicine
Cincinnati, OH

Hugh Miller, M.D.
Arizona Health Science Center
Tucson, AZ

Jonathan Weeks, M.D.
Norton Suburban Hospital
Louisville, KY

Consultants
Donald Berry, Ph.D.
University of Texas M.D. Anderson Cancer Center
Houston, TX

Consultants (cont.)

Leonard Glassman, M.D.
Washington Radiology Associates P.C.
Washington, D.C.

Scot E. Goldberg, D.O., M.B.
Women's Imaging Center
Newark, DE

Yulei Jiang, Ph.D.
University of Chicago
Chicago, IL

Joanne Mortimer, M.D., FACP
University of California
San Diego, CA

Russell Snyder, M.D.
University of Texas Medical Branch
Galveston, TX

Sheila Taube, Ph.D.
National Cancer Institute, NIH
Rockville, MD

Consumer Representative
Diana Romero, Ph.D.
Columbia University
New York, NY

Patient Representative
Musa Mayer
Woodstock, NY

Industry Representative
Elisabeth George
Philips Medical Systems
Newton, MA

Executive Secretary
Michael T. Bailey, Ph.D.
CDRH

FDA Participants
Nancy Brogdon
Director, Division of Reproductive, Abdominal, and Radiological Devices

Roselie Bright, Sc.D.
Office of Surveillance and Biometrics

Kish Chakrabarti, Ph.D.
Office of Device Evaluation

Nicholas Petrick, Ph.D.
Office of Science and Engineering Laboratories

Robert Phillips, Ph.D.
Office of Device Evaluation

Colin Pollard
Chief, OB/GYN Devices Branch

Lakshmi Vishnuvajjala, Ph.D.
Office of Surveillance and Biometrics

Ron Yustein, M.D.
Office of Device Evaluation

Sponsor Presenters
Vivian Dickerson, M.D., FACOG
University of California, Irvine

Ron Ginor, M.D.
President & CEO, Mirabel Medical Systems, Inc.

Sarah Lenington, Ph.D.
Director of Clinical Development
Mirabel Medical Systems, Inc.

A. Thomas Stavros, M.D., FACR
Radiology Imaging Associates
Denver, CO

LTC Alexander Stojadinovic, M.D.
Vice Chairman, Department of Surgery
Walter Reed Army Medical Center

Joel I. Verter, Ph.D.
Statistics Collaborative, Inc.

CALL TO ORDER

Acting Panel Chair Marcelle Cedars, M.D., called the meeting to order at 8:06 a.m. and asked the panel members to introduce themselves. **Panel Executive Secretary Michael T. Bailey, Ph.D.,** announced the two tentative panel meeting dates remaining for the year are November 13 and 14, 2006. He then read into the record the appointment of temporary voting members Russell Snyder, M.D.; Sheila Taube, Ph.D.; Donald Berry, Ph.D.; Yulei Jiang, Ph.D.; Leonard Glassman, M.D.; and Scot Goldberg, D.O., M.B. A separate appointment to temporary voting status was read for Joanne Mortimer, M.D., FACP, a member of the Oncologic Drugs Advisory Committee. Dr. Bailey then read the conflict of interest statement. There were no conflicts to report.

Colin Pollard, Chief, Obstetrics and Gynecology Devices Branch, welcomed the panel and noted that FDA approved the PMA for the Adept 4% icodextrin adhesion reduction solution on July 28. Today's meeting is convened to review pre-market approval application (PMA) P050003 for Mirabel Medical Systems' T-Scan 2000 ED, which is intended as a complement to clinical breast exam (CBE) for detection of cancer in women ages 30-39 at average risk for breast cancer. The PMA was reviewed by the Radiologic Devices Branch because the branch reviewed the first generation device, has historically dealt with all diagnostic devices for breast cancer regardless of the specific technology used, and has extensive experience with electrical impedance.

OPEN PUBLIC HEARING

Ronald Wapner, M.D., Columbia University, discussed the paradigm of screening. The purpose of screening is to identify subpopulations at higher risk so they can be subjected to additional diagnostic testing or evaluation. Screening tests are

generally used on healthy patients and should be relatively inexpensive, easy to use, and reliable. The disease screened for should be relatively common and have a significant outcome if left untreated. There must be a beneficial intervention for those identified as having the condition, and there needs to be reasonable sensitivity and specificity so as to identify an appropriately sized cohort.

Dr. Wapner said the T-Scan 2000 ED met all of the criteria for a screening test and should be used in low risk populations. He then talked about the history of prenatal screening for genetic disease. One important step was making physicians and patients understand that a positive screen does not mean that one has the disease.

Mark Akin, M.D., **Austin Area OB/GYN,** discussed his own clinical experience with the device as a principal investigator for the specificity arm. He noted that CBE detects less than ten percent of cancers of less than two centimeters in women under age forty with the result that cancers are more advanced when they are finally diagnosed. There is a clear need for improved screening for this age group. The T-Scan screening can be easily integrated into annual exams, does not require additional appointments or follow-up, and offers significant improvement in screening of young women.

Dr. Glassman asked about the screening of women 30-39 who had a first degree relative with a history of breast cancer. Dr. Akin replied that most of those patients are screened using mammography starting at 35, or if the relative's cancer occurred at a very early age, ten years prior to the patient reaching that age. Ms. Mayer pointed out that the American Cancer Society's data said that patients in the target population make up only 4.5 percent of cases as opposed to the 15 percent quoted by Dr. Akin, who said he would have to check his reference. Dr. Romero asked how he had measured whether patients

with a positive result had expressed any undue anxiety. Dr. Akin responded that it was by personal observation.

Cindy Pearson, Executive Director, National Women's Health Network, noted the importance of breast cancer screening in young women and said it should be painless and without intrinsic risk. She also noted that the sample was rather small and that a lot of statistical modeling was used to determine the sensitivity and specificity of the device. It appears that many women would receive a false positive and few would benefit from the screening. Ease of use, the ability to perform the screen in the doctor's office, lack of pain, and fast response are assets of the technology, but they will lead to widespread use, so there needs to be a solid demonstration of effectiveness.

SPONSOR PRESENTATION

Ron Ginor, M.D., President and CEO, Mirabel Medical Systems, Inc., introduced the sponsor presenters. Although only one in 229 women will develop breast cancer by age 40, there are more breast cancers in that population than there are cervical cancers in America or babies born with Down syndrome. A multi-center pivotal trial was conducted at thirty centers with nearly 3,000 patients, and a five year multi-center U.S. Army study is underway with a goal of enrolling 15,000 patients.

The device is not a replacement for mammography or other imaging but simply a risk assessment tool. All women offered the T-Scan are between 30 and 39, asymptomatic, and have no known risk factors. The recommendation following a positive result is a single imaging; unlike the BRCA, for example, the T-Scan is not a lifelong risk assessment. The aim is to identify roughly five percent of the target population who are at approximately five times the risk expected for the age group.

The device uses Ohm's uncomplex law that if voltage and current are fixed, changes in resistance will be measurable. Resistivities of various tissues have been identified, and patients falling outside the normal parameters are recommended for additional screening. The prior device was determined by the FDA to be safe and effective and to have sensitivity for cancer. Following its approval, studies showed that the technology had particularly good sensitivity for the smallest lesions.

The device cannot be used on women with abnormal CBE since they have already been identified to be at risk, nor can it be used on pregnant women. The device requests information obtained in CBE, and if any of it is abnormal, the report generated says the patient needs additional follow-up irrespective of the test results. The Gail model is also used to help elicit any other potential risks. A circuit of tightly controlled voltage and current enters the patient, returns to the device, and is immediately analyzed. Although there is something that resembles an image, it is merely a way to ensure that contact has been made with all of the nine areas.

LTC Alexander Stojadinovic, M.D., Vice Chairman, Department of Surgery, Walter Reed Army Medical Center, and Memorial Sloan Kettering, noted that his views do not reflect the official views of the United States government. The primary outcome variable was relative probability of having cancer at exam, calculated based on study estimates of specificity and sensitivity as well as published data on disease prevalence within the general target population. The sponsor working with FDA set the success threshold for relative probability at two, which is representative of the current standard of care. The specificity arm cohort was healthy asymptomatic women ages 30-39; it was assumed that all positive exams were false positives, so there may have been a

few true positives that were overlooked. The sensitivity arm looked at women 30 to 45 already determined to need breast biopsy based on an apparent abnormality, and the women were pre-menopausal to assure that all breast tissue was similar. This enriched population was used due to the low probability of identifying a CBE-negative tumor in young women, and the data obtained from pre-menopausal women 40-45 are applicable to the intended use population based on a previous study of impedance characteristics. A conservative estimate of prevalence in the general target population of 1.5 cancers in 1,000 was used.

There were 1751 per protocol exams in the specificity arm; specificity was 94.7 percent. Even at the low end of the confidence interval, the success threshold was met. There were no significant differences found in an analysis of relevant covariates.

There were 390 per protocol examinations in the sensitivity arm; 87 cancers were confirmed through biopsy. Technical difficulties related to the fact that investigators were blinded to test results accounted for 65 of the 69 exclusions for technical difficulties. These were caused by two defective devices at a single site; because of blinding the problems were not identified until quality assurance and monitoring visits. Covariate analysis showed no significant differences between groups. There was a tendency, though not statistically significant, towards increased sensitivity for smaller lesions. The overall sensitivity was 26.4 percent, and the majority of cancers were infiltrating.

The estimate of relative probability was 4.95 based on the target population prevalence of 1.5 per 1,000. This suggests that a woman with positive T-Scan is almost five times more likely to have cancer than an average risk woman.

Joel I. Verter, Ph.D., Statistics Collaborative, Inc., began by discussing enrichment of the sensitivity arm cohort. Without the enrichment, the sensitivity arm would have required almost a quarter of a million patients in order to detect the same number of cancers. The FDA made a calculation of specificity based on the sensitivity data, but Dr. Verter said that was not appropriate because those identified for the sensitivity arm already had an indication of breast pathology, so this calculation does not provide a relevant and usable false positive rate.

Using the specificity and sensitivity from the study but assuming a lower prevalence of .05 percent, the relative probability would be marginally increased and the success criterion would still be achieved. Holding specificity constant, assuming prevalence of .15 percent, but varying sensitivity, using the low end of the confidence interval, limiting the calculation to those 30-39, or only looking at women in the U.S., the relative probability would still meet the success criterion. Varying specificity to the highest and lowest observed levels and using the sensitivity determined in the study and prevalence of .15 percent, the criterion is still met.

As for pooling, Mirabel monitored the various sites and saw no evidence the study was being conducted in a non-uniform manner; furthermore, there is no interpretation required for the binary outcome of the T-Scan. Low power, Type 1 error, and post hoc analysis are concerns, but any heterogeneity suggested by the data should be investigated by all concerned. Looking at subgroup analyses in the specificity arm, in all cases specificity around 90 percent and anything greater than or equal to 87.5 will still yield relative probability over 2. All data for the specificity sites can be pooled.

In the sensitivity arm, there were no subgroup differences based on patient characteristics, study design, machine, medical practice, patient management, or examiner bias. FDA noted a possible difference between the U.S. and Israel, but looking at all the sites no differences were found. Furthermore, if the Israeli patients were excluded the relative probability would still exceed 2.

FDA did a logistic regression using an odds ratio, which the agency argues is an overestimate of relative probability, of 2.6. However, FDA misclassified some women based on family history; using only first degree relatives, one gets an odds ratio of 1.5. Also, the 2.6 number indicates that even after adjustments a T-Scan positive woman will still be 2.6 times as likely to have breast cancer.

Vivian Dickerson, M.D., FACOG, University of California, Irvine, began by introducing the sponsor's expert panel. Summarizing their conclusions, she said the study was large and well designed; it was appropriate to exclude post-menopausal women and to enrich the sensitivity arm with pre-menopausal women ages 40-45; safety and effectiveness data were sufficient; and the results can be generalized to the target U.S. population. Dr. Dickerson then discussed CBE for women under 40. Most cancers in this age group are self detected, and five-year survival is lower than for older women. Anxiety and fear are already common because of the lack of effective screening. T-Scan has all the attributes of a screening tool, is safe and effective, and would help identify 3,000 to 5,000 cancers that would otherwise be missed.

A. Thomas Stavros, M.D., FACR, Radiology Imaging Associates, Denver, Colorado, talked about the similarity of breast tissue of women in their thirties and those in the early forties. There is no point at which breasts go from entirely dense to entirely

fatty. Previous studies have grouped all pre-menopausal women under 50 together. Looking at the risks of mammography, Dr. Stavros pointed out there are other imaging methods with no risk, and there are virtually no direct risks associated with the T-Scan. Furthermore, positive T-Scan would not lead to a lifetime of risk but rather a single workup in the thirties, and nothing at all would need to be changed in care after age 40.

Dr. Ginor said that it was a large study that offers reasonable assurance of safety and efficacy. The primary endpoint was developed in consultation with FDA and other experts and was exceeded almost any way one looks at the data. There is no product safety concern, and the additional mammography risk is negligible. A five-year study is underway to more thoroughly address various issues.

The algorithm was developed using only 18 cancers, and the mean sensitivity was initially about 34 percent. Although there are now better methods for algorithm development, the device was already recognized as safe and so was moved to clinical study. The sponsor is confident the algorithm is stable and will ensure that it becomes more and not less stable as more data is collected.

Subgroup analyses did not alter the conclusions of the study. The level of risk identified significantly exceeds the current standard of care at which additional screening is offered. As for enrichment, age in and of itself should not have an impact on the breast tissue, so long as all are pre-menopausal.

Dr. Ginor addressed the issue of blinding and technical difficulties and said that the high degree of technical failures seen in the sensitivity arm would not occur in clinical practice because the device would provide feedback indicating that it was not working properly. As for the risk of mammography, Dr. Ginor said that mammographic

screening of T-Scan positive women is more than three times as effective as the current standard of care.

Dr. Glassman asked whether a positive T-Scan result would mean someone was positive for life and should receive annual screening. Dr. Ginor replied that it is a physiological exam at a particular time and thus it would be a one-time, not lifelong, risk. There is not data to support that the patient should be treated differently for the rest of her life.

Dr. Mortimer asked what a normal breast exam was; whether there are differences in impedance more likely to correlate to a positive result; and about the lack of lobular carcinoma in situ (LCIS). Dr. Ginor said CBE was considered normal if the patient would not have been sent to additional workup if not for T-Scan. One LCIS was found, but the sponsor and FDA had agreed that only true malignancies would be considered as such in the study. With regard to particular impedance differences, Dr. Ginor said that changes in cellular fluid in and outside of cells were of particular note.

Dr. Hillard asked for the definition of menopause. Dr. Dickerson said the study definition was six months of amenorrhea, which is more stringent than the twelve months generally used in practice, with no hormonal suppression of periods.

Dr. Snyder asked about reproducibility of the data in a single patient. Dr. Ginor said they had conducted a repeatability study which showed no changes. Dr. Glassman asked whether some of the women in that study were positive, and Dr. Ginor replied that one woman was positive repeatedly.

Ms. Mayer asked whether they looked at stability of impedance over the menstrual cycle. Dr. Ginor said that had been done as part of the approval for the prior

device and there are differences depending on time in cycle. But with the current device the threshold is too far from baseline for menstrual changes to change the result. Ms. Mayer asked whether there was less sensitivity with the raised threshold, and Dr. Ginor replied not with the current device.

Dr. Taube asked why a single site accounted for 93 percent of failures due to technical difficulties, and Dr. Ginor reiterated his comments that the site had two broken devices and that the error messages were not visible to the clinicians due to blinding. Dr. Taube then asked how many women in the sensitivity study had refused to participate. Dr. Ginor clarified that often there simply was not time because women are increasingly scheduled for biopsy the same day, whereas in Israel there is a lot more time between when they are scheduled and when the biopsy takes place. He suggested they could provide an answer after a break.

Dr. Snyder asked for further clarification of the technical difficulties. Dr. Ginor said that there was concern about biasing surgeons prior to biopsy and that all visual feedback from the device was eliminated, meaning there was no way users could know if there was a problem with the device. However, in clinical practice, the device would never be blinded in this way.

Dr. Miller asked about any differences in the type of tumors suspected in those 30-39 versus those 40-45; whether the device is more sensitive in smaller breasted women; whether there was enough ethnic diversity; and about factors that may influence impedance. Dr. Cedars asked the sponsor to hold off on answering to ensure that all questions could be asked.

Dr. Berry asked whether 1.5 per 1,000 was the cumulative proportion of women who will have breast cancer in their thirties. Dr. Ginor said the cumulative effect was the NCI data of one in 229, nearly 4 per 1,000. Dr. Verter said 1.5 per 1,000 was the point prevalence. Dr. Berry said the SEER figures were less than that, and Dr. Verter said SEER was incidence, not point prevalence. Dr. Berry maintained that the rates were much less than that.

Dr. Berry then asked about blinding and operator effect and whether the operators knew the women were heading to biopsy. Dr. Ginor said that all the women were known to be going to biopsy but that there was no way any operator could force the device to read one way or another. Also, only two in ten biopsies find cancers, so there would be no way to know in advance whether someone had cancer. Also, if an operator for whatever reason decided to run a second exam, it would have shown up as an additional case for the same patient. Dr. Berry inquired further about a reproducibility study across operators, and Dr. Ginor said there was no significant operator effect. **Sarah Lenington, Ph.D., Director of Clinical Development, Mirabel Medical Systems, Inc.,** said that occasionally different operators got different results for the same patient, but these cases were randomly distributed across operators.

Dr. Berry pointed out that data from FDA showed that none of the thirteen cancers in U.S. women were detected. Dr. Weeks asked why the sensitivity seemed better with smaller lesions; whether body mass index (BMI) affected performance; and whether there was a significant difference in BMI between the U.S. and Israeli subjects.

Dr. Cedars reiterated there would be time later for additional responses, and Dr. Bailey suggested the sponsor should respond to Dr. Berry's last comment.

Dr. Ginor said they had detected cancers in the U.S. but that one could make the argument they had not if the subgroups are broken down and patients who should have been included are eliminated. Furthermore, the study was designed as an international multi-center study, and it should make no difference specifically where certain data come from unless there is reason to believe there are differences in physicians, patients, or the practice of medicine. He stressed that the study was uniform across both countries.

Dr. Goldberg asked how many of those who tested positive were subsequently confirmed to have a cancer; about the 55 patients excluded for technical difficulty; whether those 40-45 also underwent routine screening mammography; and whether the nine areas of the breast varied with variations in breast size. Dr. Romero asked about the lack of racial/ethnic representation in the sample and on what efforts the sponsor made in that regard. Ms. Mayer asked whether the 1.5 per 1,000 ratio excluded those with positive CBE or family history and about the 88 percent specificity number for black and Hispanic women.

Dr. Hillard asked about assessment of the axillary tail of the breast and whether it differed in women with different breast sizes. Dr. Taube asked if the sponsor had looked at data indicating better outcomes if tumors are found stage by stage in younger women. Dr. Berry asked about the estrogen receptor (ER) status of the cancers detected by the device.

FDA PRESENTATION

Nancy Brogdon, Director, Division of Reproductive, Abdominal, and Radiological Devices, stated that neither the panel nor the agency can take economic considerations into account and suggested talking about risk rather than cost.

Robert Phillips, Ph.D., Office of Device Evaluation, restated the indications for use and said that CBE is the only standard of care currently recommended for the target population. He introduced the agency's reviewers.

Kish Chakrabarti, Ph.D., Office of Device Evaluation, discussed the device description and operation. The device does not show or identify the location of any suspicious regions; it provides a binary outcome of positive or negative.

The previous device, the T-Scan 2000, was approved as an adjunct to mammography with equivocal Bi-RADS assessment of 3 or 4, not for cases with any indications for biopsy, and uses a different frequency range and algorithm. It also produces an image.

The current device complies with IEC 60601-1 and 60601-1-2. It performs pre-scan safety tests when it is turned on, and there are acceptable software safety tests. Biocompatibility and animal studies were conducted for the previous device, and there was no need to repeat these studies for the current device.

Nicholas Petrick, Ph.D., Office of Science and Engineering Laboratories, discussed preclinical studies with particular emphasis on algorithm stability. The device takes two impedance measurements at 17 frequencies in nine sectors for a total of 306 measurements per breast, and with such a large number there is potential for instability in the algorithm.

The algorithm training process used a training data set or learning group. Dimensional reductions are performed on the 306 measures, weights are determined for the classifier, and a threshold is selected. These help determine the stability, as do the number and quality of the training cases used in algorithm development. Stability

analysis is important to determine if the performance of the device may be due to a fortuitous choice of training data.

T-Scan uses a non-adaptive algorithm. Software revisions may include a new algorithm, potentially affecting performance, and it is possible for performance to decrease with additional training. The training data consisted of 65 cancers and 754 non-cancers. The verification data consisted of 18 cancers and 691 non-cancers and were limited to patients under 45 years of age. The validation group consisted of 12 cancers and 263 non-cancers from patients under 45.

One approach to stability analysis is the bootstrap method, a simple yet powerful Monte Carlo method. The sponsor bootstrapped the learning group with 100 partitions and calculated dimensional reduction, classifier weights, and cutoff threshold which were then used to estimate test performance for the verification and validation data. The sponsor also estimated test variability for these datasets.

The analysis indicates that the algorithm is not unstable, but training variability is not trivial. Dr. Petrick reminded the panel that the other speakers would talk about test confidence intervals based on pivotal study data but that the total variability associated with the algorithm would be somewhat greater.

Ron Yustein, M.D., Office of Device Evaluation, presented some of the clinical data. The device was considered to be non-significant risk, so no formal IDE was submitted, though there were pre-IDE meetings prior to the start of the study. FDA had some concerns about estimating sensitivity and specificity from different study populations but agreed it was a reasonable approach. Due to low disease prevalence, FDA agreed it would be acceptable to enrich the sensitivity arm, but the agency did not

specify the level of enrichment. FDA requested a breakdown of the results of patients aged 30-39 versus those 40-45 to see if there was less sensitivity in the younger patients. The agency agreed that relative probability greater than or equal to two would be reasonable and clinically meaningful, but the study and success criterion were proposed by the sponsor and agreed to by FDA.

Specificity results showed some statistically significant variations based on bra size, race, and country of origin. In the sensitivity arm, nearly 60 percent of those enrolled were aged 40-45; over 80 percent had abnormal CBE; and one in seven had positive family history. Sensitivity results showed some non-significant variation based on bra size and hormone use. In the U.S. sensitivity was 11.5 percent, and in Israel, 32.8 percent. In the intended age group, sensitivity was about 19 percent versus 32 percent in the 40-45 year old group. Of the 87 cancers used in calculating sensitivity, only four met all criteria of the intended use population, with a sensitivity of 25 percent.

Though the sponsor's statistician said there were no statistically significant differences among sites for sensitivity, breaking it down differently one sees that most of the U.S. sites had a sensitivity of zero. Forty-four patients were excluded for some reason; if they were added back in, overall sensitivity would be about 23 percent.

With regard to technical issues, it appears that there were two sites with patients excluded for technical problems, RFW and RJG. Nineteen patients with positive biopsy cancer were lost, and all were reported to be T-Scan negative. Six were in the intended patient age group. Seven post-menopausal women with cancer were not included in the analyses, but it can be argued they should have been included since the original protocol did not specifically exclude such women (24 post-menopausal women were enrolled in

the sensitivity arm), the indications do not specifically exclude them, and post-menopausal women, though few, were enrolled in the specificity arm.

Including post-menopausal women only slightly changes sensitivity from 26.4 to 25.5 percent. However, looking at the primary endpoint with regard only to U.S. patients, although the relative probability remains above two, the lower bound of the 95 percent confidence interval goes below one. Breaking the data down by ethnicity, the relative probability for African Americans is 2.41, and the lower bound is likely to be below two. As no cancers were detected in Hispanics, Asians, or American Indians, sensitivity is zero, and relative probability cannot be calculated.

The sponsor came up with .734 percent positive predictive value (PPV), meaning that one in 136 T-Scan patients are at risk for cancer, significant compared to one in 167 based on the general population, but the PPV calculations assumed mammography would detect 100 percent. If that number were around 70 percent, the ratio would be one in 194. Although relative probability is not affected much by a change in prevalence, PPV is. For a prevalence of .05 percent PPV would be one in 400 T-Scan cases.

Dr. Yustein discussed some of FDA's concerns as well as some additional data from published articles.

Lakshmi Vishnuvajjala, Ph.D., Office of Surveillance and Biometrics, outlined the pivotal study and highlighted areas of interest. FDA has no concerns about the specificity computed from the specificity arm, but there is spectrum bias in the calculation of sensitivity since the group of patients was unlike those actually indicated. Changing prevalence from .15 to .05 percent increases the ratio of false positives to true positives by a factor of four, but relative probability hardly changes. In the specificity

arm, some baseline characteristics are significantly different between the U.S. and Israel. The numbers are smaller in the sensitivity arm, but some factors are still significantly different; in particular, 31 percent of U.S. patients were CBE negative compared with 54 percent in Israel.

Comparing data from the two countries is not really subgroup analysis; it is routine to look at site differences as well as differences between U.S. and foreign data. In the 30-39 age group of U.S. women, no cancers were T-Scan positive.

The odds ratio is more amenable to statistical calculation than relative probability and can be shown mathematically to be always greater. Five factors were included in a logistic regression to estimate their effect on incidence of cancer; either being T-Scan positive, post-menopausal, or not using hormones has an odds ratio with lower bound less than two. Only being in Israel or having a family history has a lower bound of greater than two. This logistic regression was also done for those 30-39 with similar results. The primary endpoint does not allow for all of the competing effects in the prediction of cancer, and the relative probability is higher for the combined population than it is for either the U.S. or Israeli populations. One reason may be the way the two arms are combined. The separation of the study into two arms under different protocols may have unintentionally complicated how sensitivity and specificity can be consolidated into a single analysis.

Roselie Bright, Sc.D., Office of Surveillance and Biometrics, discussed the risk benefit analysis. FDA believes it is important to consider risk/benefit from different perspectives. There were three assumptions in the sponsor's benefit analysis. First was the prevalence of cancer, and FDA verified that estimates between 0.00017 and 0.0015

do not affect the calculations. Second was the estimate of specificity; FDA used the overall estimate as well as a low estimate of 88 percent found for African Americans and Hispanics. The third assumption was the estimate of sensitivity; FDA repeated the sponsor's benefit analysis using four values: 26.4 percent as used by the sponsor; 10.3 percent, calculated from all U.S. data; 5.6 percent, all U.S. women with negative family history; and zero percent, taken from CBE negative U.S. women age 30-39.

Relative probability declines as sensitivity declines. Relative probability of one would occur if women were randomly selected to undergo further screening, and less than one would indicate that the selected patients are less likely to have cancer than the overall T-Scan population.

FDA based its risk/benefit method on that used by Feig et al. FDA calculated there would be 14 deaths per million mammographic examinations of women age 30-39. Rather than lives saved, FDA calculated cancers detected in one million T-Scanned women, which would be one million times the presenting breast cancer prevalence times T-Scan sensitivity times the sensitivity of mammography. Dr. Bright explained how FDA estimated these values. The most favorable scenario, that calculated by the sponsor, would result in net benefit of 277.2 cancers detected per 0.7 deaths caused; the least favorable would result in 4.3 cancers detected per 0.7 deaths caused. Depending on the actual specificity, 53,000 to 120,000 women per million would have positive T-Scan and negative mammogram. The FDA method shows that net benefit is highly dependent on several factors in the intended use population.

Dr. Yustein summarized the FDA's presentation and outlined the issues FDA would like the panel to consider.

Dr. Mortimer asked about the 14 cancers caused per million mammograms, and Dr. Bright said that when you look at the number of mammograms needed to find one cancer, the number of deaths caused is negligible.

Dr. Berry asked how they came up with relative probability of two and said it did not make sense to have a constant factor of two for everyone aged 30-39. Dr. Bright thought the reason had to with the guidelines of the various cancer societies and that the logic was not to get women to the risk of a 40 year old but rather to compare those family history positive versus negative. Dr. Berry said that if one accepts two for a 39 year old that there should be a much higher number for a 30 year old. Dr. Bright agreed there was a lot of variation across the range 30-39 but said there was not solid data on the actual rate for each year and the effect of risk factors for each year.

SPONSOR RESPONSES

Dr. Cedars asked the sponsor to respond to unanswered questions. With regard to how many women refused to participate in the study, Dr. Ginor said there was no way for them to have a log of every time a patient was asked and refused; he said there were two women who started the exam but did not complete it due to time constraints. As to any differences in the cancers found in the 30-39 year olds versus those over 40, there was not a difference in the types of lesion found. Dr. Ginor said they were still trying to get a breakdown of grade and stage.

There was a difference in bra cup size between the two countries; the size in Israel was smaller. However, even with the largest size the endpoint was still met, though not as well. There is no reason to believe the device does not work in large breasted women, although it is hard to say conclusively given the small representation of those with size D

or greater. Another question related to bra cup size and BMI; the sponsor did not look at that but expects to in the ongoing multi-year study.

As to the types of malignancies by ethnicity, there were too few cases to break that down. The sponsor hopes to glean additional information on racial and ethnic diversity from the U.S. Army study. The sponsor used U.S. Census data to extrapolate results for various ethnicities. Moving to the hormonal milieu and possible effects of skin conditions, Dr. Ginor said that with the prior device's thresholds such factors did have an effect but that with the current device that is not the case.

Regarding the percentage of T-Scan positive women who went on for mammography, the sponsor agreed with FDA it was not appropriate to dictate or follow management given the unproven nature of the device. Responding to Dr. Yustein's comment that two sites had technical difficulties, Dr. Ginor said there were two devices at a single site.

Regarding a question about the nine areas of the breast and another about some of the more complicated areas where one would need to look for lesions, Dr. Ginor said the device was intended to measure the behavior of the breast tissue and identify areas different than expected rather than identify lesions. On the topic of representative distribution of ethnicities, Dr. Ginor said that was not something the sponsor could do in this study but that they expect to in the large ongoing study. The sponsor did not collect information on ER positivity from biopsy reports. Dr. Ginor emphasized that the device was regarded as safe based on the prior device and that efficacy was the concern. He agreed that FDA did not set the primary endpoint

Dr. Glassman inquired why there were only two patients at George Washington University Hospital. Dr. Ginor said it is a high flow center where it was hard to test women before biopsy. Although the test itself only takes six minutes, filling out CRF and getting appropriate approval from the patient takes almost an hour.

Dr. Jiang reiterated a question about higher sensitivity for smaller cancers. Dr. Ginor said there were two theories: that large lesions typically have a central area of necrosis where the impedance level rises such that one cannot see the difference; and that measurements by Davies appear to show that smaller lesions concentrate the flow of current resulting in a recognizable signal density. Dr. Jiang asked about the smallest cancers detected. Dr. Ginor said that 2 to 3 millimeter lesions had been found but that without some spiculation or calcifications they probably would not have been.

Dr. Berry asked whether the sponsor agreed that of the four cancers detected in the intended use population, only one had been detected by the device. Dr. Ginor said he was perplexed given that the study was enriched in such a way as to provide a sample that was representative of the intended population and reiterated that there is no reason to believe that breast tissue changes when a woman turns 40. Dr. Berry agreed but said he was bothered by enrichment in terms of CBE or family history positive. Dr. Ginor said that the data had been biased against the sponsor by the inclusion of palpable lesions since the device performs better with non-palpable lesions. Dr. Berry asked how many cancers there were simply restricting it to CBE and family history negative patients including those 40 and over. Dr. Ginor said it was a good question that he hoped they would be able to come up with an answer for.

Dr. Mortimer asked about lesion precursors among the benign biopsies. Dr. Ginor agreed it would be good to be able to identify those types of risks but said the analysis was not done in order to keep the study as clean as possible. Published papers have shown a significant rise in positive T-Scan results for benign, pre-malignant, and malignant masses. Dr. Cedars asked if that data had been provided, and Dr. Ginor said he did not think so given that all he had was an abstract published by unaffiliated physicians.

Returning to a previous question, Dr. Ginor stated that there were fifteen cancers in women of all ages who met the other criteria of the target population and that five of them, or 30 percent, were T-Scan positive.

FDA QUESTIONS AND PANEL DISCUSSION

1. **The primary effectiveness endpoint of the pivotal study entailed using estimates of prevalence, sensitivity, and specificity to calculate the probability that a woman who is T-Scan positive has cancer relative to a randomly selected woman from the general target population. The success criterion was set at a level of 2 or greater. Using a sensitivity of 26.4%, a specificity of 94.7%, and a cancer prevalence of 0.15%, the sponsor obtained a "relative risk" or probability of 4.95 (95% CI 3.16; 7.14) thereby meeting the pre-defined endpoint for success. FDA, however, calculated the sensitivity of the device in different subgroups to range from 0% (U.S. cancer cases under the age of 40) to 25.5% (all women regardless of age or country of origin). FDA also calculated the prevalence of breast cancer in the target population to be significantly lower than the sponsor, in the range from 0.017% to 0.054%, depending on various assumptions. In addition, FDA found that the specificity varied significantly between study arms and for several covariates and subgroups within each arm of the study.**
    a. **Please discuss the clinical significance of the primary effectiveness measure and result obtained by the sponsor.**
    b. **As the values chosen for sensitivity, specificity, and prevalence may greatly affect the results of these calculations, including whether the primary endpoint is met, please comment on what you believe reflect the most accurate estimates for each of these parameters.**

One panel member said that the primary endpoint was too low and should have been associated with age. Another said a relative probability of two is also the risk for having a first degree relative with breast cancer and that risks are not typically broken down year by year. One panel member suggested that someone who tests positive would continue to test positive and thus would enter into annual screening, as opposed to the periodic

screening that someone with a first degree relative would enter into, and was uncomfortable with that given the prevalence of the disease. Another member agreed and said it was likely that one of the mammograms such a patient would then undergo would be positive and that the resulting biopsy would indeed carry risk; also there is not data to support better outcomes when cancer is found at a very early stage versus only somewhat later. A panel member pointed out that the sponsor does not advocate that mammogram is the only approach nor that those who test positive should enter into a routine screening process.

Dr. Cedars suggested that it should be known what would be done before the device is used on a wide scale and that there should be discussion on prevalence given its impact on effectiveness. One member thought patients testing positive would get MRIs and a lot of negative biopsies. Another panel member was concerned that the device might encourage physicians to avoid their responsibility to explain the reality of a woman's risk given the incidence. Another agreed but thought that patients rather than physicians would be more likely to want rigorous follow-up for a false positive. One panel member thought that women would be negatively impacted by a false positive and said that the device would do much more harm than good. There was some concern about false reassurance for those who test negative but do have a cancer and also about the potentially unending anxiety of those who are T-Scan positive but mammogram negative.

Dr. Cedars asked about the impact of covariates and whether they should be included in the analyses. A panel member thought they should have been included and thought the enrichment was quite acceptable.

2. **The T-Scan device is intended to be used in women aged 30-39 who are negative for both Clinical Breast Exam (CBE) and Family History. Due to the relatively low prevalence of disease in the intended population, FDA agreed to enriching the sensitivity arm with subjects outside these criteria to assist with patient accrual. In order to identify a cohort of biopsy positive women (i.e. the cohort needed to calculate sensitivity), the sensitivity arm included women who were undergoing a biopsy due to an earlier positive screening. In addition, the sample was enriched with women age 40-45 (382 pre-menopausal and 24 post-menopausal) to ensure a sufficient sample size. Of the evaluable cancer patients used to determine device sensitivity (FDA's per-protocol analysis), 61% (57/94) were over age 39, 81% (76/94) had an abnormal CBE, and 34% (30/88) had a positive family history. Only 5% (4/88) of cancer positive subjects in the sensitivity arm were consistent with the indications for use statement. Please discuss whether you believe the degree of enrichment of the sensitivity arm affects the interpretation of the final results of the study and their applicability to the intended target population and if so, how.**

Panel members generally agreed that the enrichment was appropriate but thought the enrichment group was too large a percentage and that there were not enough cancers, particularly in the intended use group. Panel members were also concerned about the apparently low sensitivity for those 30-39. One panel member expressed frustration that a larger sample was not obtained because of the time and expense required to enroll more women. Dr. Cedars wondered if the prevalence of cancer was greater in women 40-45 than 30-39. One member thought the age of the tumor in older patients was more of an issue than the prevalence. Another member thought that prevalence would have an impact on PPV, but another said that PPV was calculated based on data from the 30-39 year olds. Another member said it was unfortunate there was not longer follow-up for pre-malignant lesions.

One member said that modified incidence, which is lower, also becomes important after the first year and that it would make PPV lower after the first year. A member asked about the actual number of exams done and pointed out that the labeling did not say annual but recommended testing whenever CBE is done.

The sponsor emphasized that the indication is not for repeated additional follow-up for those who test positive. For prevalence to significantly turn into incidence you

need 100 percent sensitivity and use of the product for all women in the U.S. within a relatively short period of time; also, unlike other situations, there will be new women coming into the population at age 30. A member asked whether someone who tests positive one year but negative the next would be screened again. The sponsor reiterated that T-Scan measures something specific and is a one-time screening. A panel member asked if it was possible for T-Scan to pick up a smaller lesion than a mammogram can find. The sponsor said it was indeed possible but needed more data to be able to say that routine mammograms would be appropriate for those who test positive. The sponsor proposed that CBE is still relied on because it is virtually impossible to do studies of the magnitude that everyone wants given the time required.

One panel member agreed that it was likely that a patient would continue to be T-Scan positive and wondered if patients might want more than annual follow-up. One panel member asked if it was correct that the chances of having a cancer with a positive T-Scan were better than those of finding a cancer with a mammogram. Another member said that T-Scan has greater specificity but lower sensitivity than mammogram so there will be more false negatives.

Summarizing the discussion, Dr. Cedars stated there was some discomfort with the applicability of the enrichment population but that the panel was generally willing to accept the results.

3. The pivotal study was conducted at multiple sites in the United States and Israel. As shown in the table below, the sponsor's per-protocol analysis (without post-menopausal women) showed no statistically significant difference in device sensitivity between countries while the FDA's per-protocol analysis (including post-menopausal women) did.

	Excluding Post-Menopausal Women in Se Arm	**Including Post-Menopausal Women in Se Arm**
Sensitivity in U.S.	**11.5% (3/26)**	**10.3% (3/29)**
Sensitivity in Israel	**32.8% (20/61)**	**32.3% (21/65)**

Please discuss the differences in clinical outcomes between the results for U.S. subjects and Israeli subjects and whether you believe the results from the two countries are poolable.

Panel members generally agreed that it was appropriate to pool the data as per the study design. However, most panel members expressed some level of concern about the apparent but largely unexplored differences between the patients in the two countries. One panel member highlighted the uncertainty in estimating the sensitivity. Another panel member was concerned about blanket use and thought the data suggested there may be subgroups at much higher risk.

4. **Eleven percent (11%) of patients (65/597) were excluded from the sensitivity arm due to technical difficulties with the device. Of the 37 cancers excluded from the sensitivity arm, 51% (19) were eliminated due to technical difficulties. All 19 of these cancer cases excluded due to technical difficulties were from U.S. sites. In contrast, only 0.7% (14/1946) of the patients were excluded for technical difficulties from the specificity arm.**

   Please discuss whether these losses due to technical difficulties introduce significant bias into the study.

Panel members generally agreed that the technical difficulties did not introduce any bias but thought the decrease in the sample size was unfortunate. One panel member thought there was potential for bias given the trend towards decreased sensitivity in the U.S. population.

5. **No device-related adverse events were reported during the course of the study. However, according to the sponsor's calculations, for every T-Scan positive patient who has cancer, additional mammograms will be conducted on 135 normal subjects. If the prevalence of disease in women 30-39 is lower than the sponsor's estimate of 0.15%, this number of additional mammograms may be significantly higher.**

   Please discuss whether you believe there are any potential risks associated with these additional mammography exams in women age 30-39, taking into account that for any given woman, the T-Scan is intended to be used on a yearly basis.

One panel member said that the risk from mammography would be negligible but that the real risk would be from benign biopsies. One panel member worried about subjecting large numbers of healthy women to a traumatic sequence of procedures given the low

prevalence but wondered about the panel's views on the actual prevalence. One member pointed out that even in the worse case scenario relative risk would be 2, corresponding to an absolute risk of about one in 400, which is in the range of patients who are routinely asked to undergo screening. One panel member said that in his analysis of SEER data it looked like the average prevalence over the decade was .0005.

A panel member was not sure it would create any undue potential risks given that a positive T-Scan would merely subject one to the same level of care as an abnormal mammogram. Other panel members disagreed, given that the intended population is not currently being screened and that women overestimate their own risk of breast cancer. Some thought the problem was that the benefit was unknown.

One panel member suggested that the formality of the questions asked as part of the procedure might be helpful and pointed out that it would really only be a five year period of additional screening based on CBE once every three years from 20-39 and baseline at 35. Another panel member said there was no such thing as a baseline at 35 and that standard care includes CBE every time the patient comes in, which may well be yearly. A panel member pointed out the increased awareness of breast cancer in young women and said that mortality had gone down more in younger age groups in spite of stable incidence.

The sponsor highlighted the difference between prevalence, used by the sponsor, and incidence, used by FDA from the SEER data. The sponsor pointed out that there is nothing else to offer these patients and that CBE offers women no reassurance given that 70 percent of the cancers are self-detected. The sponsor reiterated that the study was designed by experts with direction from FDA to assess if the device is safe and effective.

There was discussion about the usefulness of CBE. One panel member pointed out that CBE, while important, has no scientifically proven utility in decreasing the chances that patients will die of breast cancer. Others said there was data showing the effectiveness of CBE combined with mammography.

6. The sponsor has proposed the following indication for use (IFU) for its device:

> ***The T-Scan 2000 ED is indicated for use as a complement to clinical breast examination (CBE) in asymptomatic women who are 30 to 39 years of age with a negative clinical breast exam and a negative family history for breast cancer. The device detects electrical impedance changes in breast tissue that are associated with an increased risk of breast cancer. A positive T-Scan™ result provides physicians with additional information to guide a recommendation regarding further breast examination, e.g., mammography or ultrasound. The T-Scan evaluates women's risk of breast cancer at the time of the exam (current risk) and not lifetime risk.***

Please comment on whether data provided in the PMA and discussed today provide a reasonable assurance of effectiveness and safety to support this proposed indication for use. If not, are there any simple modifications to this indication which the data clearly support?

One panel member suggested that the wording of the final sentence could be improved so as to be understood by a lay public given how many times the panel had to be reminded of it. One panel member wondered why the indication was not limited to pre-menopausal women given that the analyses were thus limited. One member wanted additional data on downstream events such as biopsies, and there was discussion about whether the risks of already approved devices and procedures should come into play. One member pointed out that mammography had never been shown to be effective for women in their thirties.

Panel members generally agreed that there were no narrowly defined, short-term safety issues but that effectiveness had not been demonstrated. Some panel members agreed on the issue of safety but also thought the device had shown reasonable effectiveness for its stated purpose as a risk assessment tool.

7. Taking into account your responses to the previous questions, please discuss the overall risk/benefit profile for the T-Scan device for the intended patient population.

This question was discussed in the context of previous questions. There were no additional comments, and FDA did no request any additional information.

8. Please comment on the draft labeling provided by the sponsor.

One member suggested that the patient guide should be clearly labeled as such. Some panel members took issue with the recommendations following a positive result given the uncertainty remaining. One panel member suggested that the precautions should state that the device has not been tested on lactating women, those who have undergone chemotherapy, those with recent biopsies, and those who have had any cosmetic surgery.

Dr. Cedars asked for any additional remarks from the industry, consumer, and patient representatives. Ms. Mayer underscored that the device was intended to fill an urgent need but said that something is not necessarily better than nothing. Dr. Romero highlighted the lack of racial and ethnic diversity, especially given that women of color disproportionately suffer from breast cancer.

OPEN PUBLIC HEARING II

Carol Lee, M.D., Yale University; Chair of the Breast Imaging Commission, American College of Radiology; and Vice President, Society of Breast Imaging, expressed concern about identifying increased risk without knowing how to proceed. She said that both the sensitivity and the specificity of downstream testing should be considered. She said that the sensitivity of the device was not particularly compelling and pointed out there was no data to support that the cancers detected by T-Scan are smaller early stage cancers. She urged the panel to consider the effectiveness of the device in light of how the public generally understands that a device has been approved by FDA.

Lawrence Platt, M.D., David Geffen School of Medicine, UCLA, stated that the device had been shown to be effective based on the objectives laid out prior to the study. No screening test is 100 percent sensitive or 100 percent specific; rather, such a test should balance sensitivity and specificity. Dr. Platt also felt that the device would provide an earlier opportunity for patient education. He suggested that clinicians would determine appropriate treatment following a positive result. He said that more would be learned as the device is used and said it would be helpful.

Dr. Akin read into the record a letter from Dr. Michael Fuchsjager, Associate Professor of Radiology, Medical University of Vienna, Austria. Dr. Fuchsjager said the device identified women who should be offered additional screening thereby helping to identify cancers that would otherwise be missed. He has encountered some resistance to electrical impedance but believes it stems from the misconception that the device can be used instead of mammography or other accepted screening or diagnostic technologies. Though the sensitivity is lower than that of mammography, the technology is quite valuable in identifying risk.

David Gur, Sc.D., University of Pittsburg Medical Center, pointed out that there is not a sudden transition at age 40 in terms of the prevalence or incidence of cancer; risk changes very little. Extending the age range was the only practical way to get the number of cancers one would like to study. The cancers that would typically be found in the intended age group are related to family history and/or palpability. There are no large changes between 39 and 40 in the sensitivity of downstream procedures. They are common practices, and it should be considered whether there is any reason why the

known sequela would be unacceptable for women in their thirties but okay for those over forty.

Steven R. Goldstein, M.D., New York University School of Medicine, stated that there are 12,000 cases of breast cancer in women ages 30-39. The sensitivity and specificity of the Pap smear was not as good when it was introduced as it is today. Clinical use allows for maturation and further refinement. CBE is not effective given that 71 percent find the cancer themselves.

With regard to undue subsequent testing, Dr. Goldstein stated that cancer will be found in one out of 136 or perhaps 194 T-Scan positive women as opposed to one in 300 or 400 with mammography. Screening does not always provide a definitive diagnosis, and physicians must make patients understand this. Regarding the discussions about downstream effects, Dr. Goldstein found them to be paternalistic and hoped that such decisions would be left up to individual physicians in consultation with their individual patients.

FINAL FDA COMMENTS

The FDA had no final comments.

FINAL SPONSOR COMMENTS

Dr. Ginor said that it was very hard to find a solution for CBE improvement in women 30-39. He said he was perplexed because the study exceeded every milestone. The study assigned risk at a level greater than that at which mammography is currently offered based on one or two first degree relatives or findings of ADH. He was also perplexed that the panel members would rather go back to CBE because of anxiety or the sensitivity of the various downstream procedures. He said it was extremely unlikely the

SEER prevalence was correct for 30-39 year olds given the large jump that occurs with the first mammogram. These women have their cancer prior to turning 40.

He said the device has shown reasonable safety and efficacy. Although the device is not perfect, one can expect it to improve over time following approval as was the case with other technologies.

PANEL DELIBERATIONS AND VOTE

Dr. Bailey read the panel recommendation options and explained the definitions of safety, effectiveness, and valid scientific evidence. Dr. Cedars called for a motion.

Dr. Berry moved that the device be found not approvable. Dr. Mortimer seconded the motion. There being no discussion, Dr. Cedars called the vote. The motion passed unanimously.

Dr. Goldberg based his decision on effectiveness concerns, anxiety factors, small sample size, and short duration of follow-up.

Dr. Mortimer said that the fifteen cancers were not adequate.

Dr. Weeks was concerned about decreased sensitivity in the U.S. population and decreased specificity and sensitivity in the small numbers of minorities that were enrolled. He questioned the prevalence number of .0015 and noted that sensitivity was based on a total of 94 patients, only 29 of which were U.S. He thought there could be some bias based on the cases lost to technical difficulties. He also noted that the sensitivity figures included patients with positive CBE or positive family history.

Dr. Berry was concerned about false positives and additional procedures. He thought a relative probability of two was too low and said that it was not achieved based on some of the FDA's calculations of confidence intervals.

Dr. Glassman was mainly troubled by the small numbers but was also concerned that the prevalence was lower than 1.5 per 1,000 meaning that PPV would be very poor.

Dr. Jiang was not sure that relative probability of two was a great goal or that it had actually been met. He was unsure of the relative risk but stated that the device had great potential.

Dr. Miller said that although he did not have a problem with the foreign data, he was concerned that the conclusions drawn did not reflect site differences. He did not think it was justifiable to subject an undue number of women to potentially painful or morbid procedures.

Dr. Snyder said the data suggested the device to be a risk assessment tool but was unsure if it is a screening tool. He did not think there was enough data to know what to do with those identified as being at increased risk and hoped that the ongoing study would provide the data the panel needed.

Dr. Taube said that there was not enough data to show that the device is safe and effective and that they did not know what to do with those identified as being at increased risk.

Dr. Hillard was not convinced of the benefit of the device and had concerns particularly with regard to sensitivity, poor PPV, and the harms of false positives.

Dr. Cedars asked the panel members to state what would be needed to make the PMA approvable.

Dr. Hillard wanted greater numbers in general as well as for subgroups. She also wanted data on BMI.

Dr. Taube wanted data on the types of tumors identified as well as on the outcomes of cancers.

Dr. Snyder wanted more information on reproducibility and on what would happen with a positive result in subsequent years.

Dr. Miller wanted data on performance among ethnic groups and thought the sponsor could do some post hoc analysis of the different performance characteristics in the Israeli sites. He also wanted a better understanding of the actual prevalence in the target age group.

Dr. Jiang wanted reproducibility data from repeated scans of women and said that getting good sensitivity data was difficult.

Dr. Glassman wanted more patients, particularly those with non-palpable cancers and conceded that it would probably have to be accomplished through enrichment.

Dr. Berry agreed with the all the previous comments. He said that the ideal for getting information on types of tumors would be a mortality study but acknowledged the difficulties involved. He also wanted some quantification of anxiety levels.

Dr. Weeks agreed with all the previous comments. He acknowledged the difficulty in getting data on asymptomatic patients without masses or a family history, and he suggested a compromise might be to look at BRCA or positive family history negative CBE patients.

Dr. Mortimer was eager to learn whether those with positive results really had something there. She also wondered about any correlation between positivity and histologies classified as benign that in reality were not.

Dr. Goldberg agreed with the comments made with a focus on increased numbers.

Ms. George talked about the importance of defining protocols and endpoints ahead of time given that the panel was not satisfied with the study design and the number of patients enrolled. She also wondered if the clinicians on the panel really wanted industry to dictate appropriate follow-up.

Dr. Romero suggested that validated psychosocial measures could have been used to look at stress and anxiety.

Ms. Mayer was interested in looking at the tumor types and stages found by the device.

ADJOURNMENT

Dr. Cedars adjourned the meeting at 4:38 p.m.

I certify that I attended this meeting of the Obstetrics and Gynecology Devices Advisory Panel Meeting on August 29, 2006, and that these minutes accurately reflect what transpired.

Michael Bailey, Ph.D.
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

Marcelle Cedars, M.D.
Acting Chairperson

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