FDA's Executive Summary:

P050003: T-Scan™ 2000 ED, Mirabel Medical, Inc
For Radiological Devices Panel Meeting of August 29, 2006

I. Proposed Indications for Use

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.

II. Device Description

The T-Scan™ 2000 ED device (henceforth will be referred to as T-Scan in this document) device detects breast cancer by analyzing the differences in electrical impedance between malignant tissue and surrounding normal or benign tissue.

By applying an approximately 1 volt electrical signal via signal transmitter, the device measures conductance and capacitance over the 100 Hz-200 kHz frequency range and the resulting electric currents at each point of the 8x8 sensor array on the surface probe. The device does not produce any image but displays a green indicator if the result is negative and a red indicator if the result is positive.

A. Device Components

T-Scan is available in desktop and cart configurations. The main components are:

- an isolation transformer;
- the main console PC;
- a surface probe, which is a hand-held, multi-electrode unit that operator places in contact with the patient's breast when performing a scan;
- a signal transmitter, which is a stainless steel cylinder held in the patient's hand;
- PC input/output peripherals, which include a monitor, keyboard, and trackball, and an optional CD read-write drive; and
- a laser printer.

A commercially available, conductive gel is used with the device.

B. Device Operation

A T-Scan examination is performed after clinical breast examination. The surface probe is placed in contact with the patient's breast. The device measures tissue electrical impedance over four decades of frequencies (100Hz-200kHz), by applying an electrical signal (approximately 1 volt) via a signal transmitter held by the patient in her hand contralateral to the breast being examined, and detecting the resulting electric currents. The device detects differences in the electrical impedance between malignant tissue and surrounding normal or benign tissue based on the principle that malignant tissue has higher conductance. The averages of both the capacitance and conductivity values (over all 8x8 sensors in the surface probe) at 17 preset frequencies and at each of nine anatomical sectors of the breast are obtained from each breast. Hardware and software controls limit the voltage and the resulting current to 2.5 V and 5 mA maximum. The safety circuits are identical to the T-Scan™ 2000, approved on April 16, 1999 (P970033). This device was approved with intended use as an adjunct to mammography in patients who have equivocal mammographic findings within ACR BI-RADS categories 3 or 4.

The device analyzes multi-frequency data and produces a binary outcome of negative or positive. This binary outcome of negative or positive is defined using a subset of the impedance measurements with a trained statistical classifier. The classifier's output is thresholded to produce a binary output for each patient. The device displays a solid green horizontal line if the result is negative and a red hatched line if the result is positive. These results are based on the scan from both breasts. The device indicates a negative examination result only if the value for both breasts is below the predetermined positivity threshold. The device does not show or identify the location of any suspicious region. The device does not produce any image for diagnosis.

C. Development and Validation Datasets

In order to develop the binary classification algorithm, both training and validation cases were collected. Table 1 provides the case distribution for the different datasets utilized in algorithm development and validation. Subjects of all ages (65 cancers and 754 non-cancers) were included in the Learning group. The Verification and Validation groups, on the other hand, consisted of young (age < 45 years and below) subjects only. The Learning group was utilized for feature selection, Linear Descriminant Analysis (LDA) classifier design and threshold selection. Data was shuffled between the Learning group and the Verification group before each new classification approach was trained and verified. In order to further validate the algorithm before embarking on the pivotal clinical study, the selected algorithm was tested only once on the Validation group whose data were collected only after the algorithm was finalized. This methodology was utilized to avoid contamination between development, validation and clinical study patients. All cases in each of the three groups were mutually exclusive. To summarize the dataset:

- The Learning group was used for feature selection, algorithm training and threshold determination.

- The Verification group was part of the overall development group (Learning + Verification), with different cases from the learning group, used to initially verify algorithm performance.
- the Validation group was utilized as an independent check of algorithm performance before starting data collection for the clinical study.

Table 1: Case Distribution during Algorithm Development and Validation

	Cancer cases	Non-cancer cases
Learning (training) group	65	754
Verification group	18	691
Validation group	12	263

D. Classification Algorithm

The classification algorithm is based on LDA where a linear combination of the impedance measurements, the features, are combined to produce a single score for each breast. Each breast score was then compared to a fixed threshold. If either breast had a score above this fixed threshold, a positive T-Scan ED response was reported for the patient. The threshold, based on training, was selected to achieve a 90% specificity in the Learning group.

During a T-Scan examination, 306 impedance measurements are obtained from each breast. These measurements include the averages of both the capacitance and conductivity values (over all 64 detectors in the probe) at 17 preset frequencies and at each of nine anatomical sectors (2x17x9) of the breast (nipple sector, plus 8 additional sectors). Not all of these features are used by the classification algorithm. Instead, feature selection was employed to limit the number of features with the goal of improving the robustness of the classification strategy. The feature selection reduced the original 306 impedance features to a final set of only 26 features. The feature selection added additional complexity to the simple linear classifier in 26 dimensions. Three steps, embedded in the learning process, were responsible for the reduction in the feature space from 306 to 26. The first step selected only those individual features, with the greatest separation between the cancer and non-cancer in the Learning group. The second step further reduced the dimensionality of the parameter space by removing eigenvectors of the covariance matrix whose individual separation between the cancer and non-cancer cases in the Learning groups was small. Finally, the third step removed eigenvectors with small eigenvalues, improving the conditioning of the covariance matrix required for a stable inverse.

Once the subset of 26 features was identified, the Learning group data was utilized to estimate the coefficients in the LDA classifier.

E. Safety Tests

1. Electrical Safety

T-Scan complies with standard:

- IEC 60601-1, International Standard – Medical electrical equipment, Part 1, General requirements for safety; and
- IEC 60601-1-2, International Standard – Medical electrical equipment, Part 1, General requirements for safety, 2- Collateral standard, electromagnetic compatibility – Requirements and tests.

2. Device Safety

T-Scan performs device safety tests each time it is turned on. Tests included:

1. proper connection of the surface probe and the signal transmitter;
2. proper functioning of the system's voltage-limiting circuit; and
3. proper calculation of algorithm results

These test results were accepted by FDA.

III. Summary of Pre-Clinical Studies

A. Biocompatibility

Biocompatibility was assessed for the PMA-approved T-Scan 2000 (P97003) containing the same hand-held surface probe and signal transmitter. The current device components are composed of the same materials, obtained from the same supplier.

B. Animal Studies

The T-Scan ED consists of the same primary components and performs the same basic function, *i.e.,* electrical impedance scanning of the breast for the detection of breast cancer, as the PMA-approved T-Scan™ 2000. Therefore, FDA accepted that further animal study was not necessary.

C. Algorithm Stability Analysis

The stability of the classification algorithm architecture is related to the complexity of the feature selection and estimation of the algorithm weights and threshold, and the number and quality of the training case set. In this case, algorithm architecture refers to the combined processes used for feature selection and estimation of the algorithm weights and threshold (not a particular realization of the algorithm), and stability refers to the uncertainty in test performance for different realizations of the training case set. A more complex architecture (*e.g.*, the use of a quadratic instead of a linear classifier or a different feature selection process) leads to more uncertainty in test performance for different realizations of the training case set. More complex algorithms are vulnerable to a classic problem for statistical learning machines explained in Cover's Theorem. Cover's Theorem says that, even for linear architectures, one needs a number of samples between two and four times the

dimensionality of the feature space just to make the problem well-posed. Any one realization of the training data produces a single fixed classification algorithm, whose test performance can be evaluated with independent data.

The training variability associated with the overall algorithm architecture is of interest because it can indicate whether or not the stated performance was due to just a fortuitous choice of training and test sets, especially if that data is not representative of the true population. It is also likely that the algorithm will evolve over time as more data is collected leading to changes in the features, weights and threshold, if not the actual classifier type. One approach would be to collect new data and retest each version of the classifier, in a similar manner as in this PMA. This can be quite onerous. FDA's approach is to try and consider the technology as a whole, in pre-market, by evaluating its stability. With hardware, FDA evaluates how a result changes when the hardware system is perturbed. Obviously this makes sense because no two systems sold are exactly alike. In the case of software, FDA argues that it is also important to know how an algorithm changes when the software is perturbed, even though the software performs exactly the same way on each system. If the algorithm is insensitive or stable with respect to training, the test performance would not be expected to vary significantly with new data so that the overall technology could be approved instead of a single realization.

In summary, training variability provides a measure of algorithm complexity and its expected stability. It further provides a measure of the technology itself, over and above the particular samples utilized in the present study, by providing a measure of the uncertainty in test performance when updates are made to the algorithm.

The stability of the T-Scan algorithm architecture was evaluated by bootstrapping of the Learning group (*i.e.*, training) data and looking at the resulting variability in test performance for the Verification and Validation groups. Bootstrapping is a general tool for assessing statistical accuracy. The basic idea is to randomly draw datasets with replacement from the training data, each dataset the same size as the original training set. The multiple realizations of training data are then used to select features, design the classification algorithm and determine the cut-off threshold. This newly trained algorithm is then tested on the Verification and Validation data sets. The results of this procedure are discussed below.

Specificity and sensitivity results for the verification and validation groups based on 100 bootstrap realizations of the training data are summarized in Table 2 below.

Table 2: Verification and Validation group performance when bootstrapping the training data

Dataset	**Specificity**			**Sensitivity**		
	Mean	SD	95% CI	Mean	SD	95% CI
Verification group	90%	3%	84–96%	34%	11%	12-56%
Validation group	87%	4%	79-95%	29%	13%	3-55%

As a comparator, the variability of the test results for the single fixed training data set was also calculated. These results are summarized in Table 3 below. The

results are based on bootstrapping the Verification and Validation groups 1000 times and reporting the standard deviation (SD) in the resulting test performance. Note, this analysis is not an estimate of algorithm stability of the algorithm architecture since the training data is held constant but is instead allowing a confidence interval of test performance to be calculated. This table also includes the same 95% confidence interval (CI) for the pivotal clinical trial test data summarized later in this document.

Table 3: Verification and Validation group performance when bootstrapping the test data

Dataset	**Specificity**			**Sensitivity**		
	Mean	SD	95% CI	Mean	SD	95% CI
Verification group	93%	2%	89-97%	44%	12%	20-68%
Validation group	89%	2%	85-93%	33%	14%	5-61%
PMA, Intent to Treat	95%	-	93.7-95.7%	29%	4.5%	20-38%
PMA, per Protocol	95%	-	93.9-95.9%	31%	5.5%	20-42%

The bootstrapping results indicate that the algorithm architecture is not remarkably unstable, but also not completely robust (i.e., the results do have variability). The algorithm architecture (*i.e.*, the feature selection, algorithm training, and threshold selection processes) produces variability on the order of the test variability in the Verification and Validation groups. When the sample size in the bootstrap experiment is scaled up to give a sample size comparable to that in the pivotal clinical trial, the variability over the random selection of trainers scales to be *comparable* to the variability over the random selection of testers. Although it is not appropriate to simply add these two variances, it is clear that the total variability associated with algorithm architecture or technology, algorithm development, and testing is greater than that manifested in the straightforward calculation of the confidence intervals provided by the sponsor when accounting for both of these effects. It is likely that a large fraction of the training variability comes from the disparity in the number of cancer and non-cancer cases. Increases in the number of cancer training cases could substantially improve the stability of this algorithm architecture.

IV. Summary of Clinical Studies:

A. *Sponsor's Pilot Study*

Pilot study data were collected using an experimental algorithm. The purpose of this pilot study was to develop an algorithm for higher frequency recordings. To this end the T-Scan recorded frequencies up to 200 kHz, whereas the experimental algorithm did not incorporate frequencies above 5 kHz.

Based on the data from the pilot study, the sponsor concluded that an improved algorithm could be constructed by incorporating the high-specificity thresholds in the experimental algorithm combined with electrical impedance characteristics measured at higher frequencies (~ 200kHz). This data was also the basis for training the final binary classification algorithm utilized in the T-Scan device.

B. Pivotal Study

1. Overview

The sponsor conducted a multi-center prospective study with a study objective of specifically evaluating the association between T-Scan positivity and breast cancer risk in a target population of young women. The clinical study was designed as a two-arm trial, where one arm estimated specificity (specifically, the false positive rate) and the other arm estimated sensitivity (cancer detection rate) of the T-Scan. The Specificity Arm of this study was intended to include the population of women age 30-39. In the Sensitivity Arm, however, an expanded age range (30-45) of women was accepted in order to allow more expeditious accrual of patients.

The primary endpoint of the study entailed using these estimates of 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 population at large based on estimates of the sensitivity (Se), specificity (Sp), and the prevalence of cancer in the population (Rca). The primary endpoint of the pivotal study was to show that a woman who is positive on a T-Scan exam has a risk for breast cancer that is at least twice the expected risk in the general target population.

2. Specificity Arm

a. Introduction

The primary objective of this arm of the study was to measure the specificity (true negative) in a cohort of women who are expected to be free of breast cancer and representative of the intended use population.

b. Study Design

Study subjects consisted of 1946 women enrolled at 2 clinical sites in Israel and 15 in the U.S., who had no breast related signs or symptoms and who visited their obstetrician/gynecologist or breast center for an annual physical exam.

Those meeting the following criteria were enrolled upon signing informed consent.

Inclusion criteria:

- Women age 30-39 inclusive; and
- Not pregnant.

Exclusion criteria:

- Previous cosmetic surgery;
- Breast biopsy or surgery within three months (90 days) of the exam;
- Previous breast FNA within 1 month (30 days) of the examination;
- Breast-feeding within the previous three months;
- Presence of an electrically powered implanted device (*e.g.*, pacemaker);
- History of or currently undergoing chemotherapy;
- Palpable breast mass; and
- Known breast cancer.

Patients had a CBE by a qualified examiner (referring physician or investigator). Specific attention was paid to the CBE and presence/absence of a palpable mass. Women were also questioned regarding potential covariates such as menopausal status, hormone use, bra cup size, FHx of breast cancer, ethnicity, and age.

c. Patient Population

Of the 1946 women enrolled, 1933 had T-Scan examinations with results, of which 1751 were completed per protocol. Exams were excluded based on: patients not meeting the eligibility criteria (179); technical difficulties during the T-Scan examination with no exam results (11); unreliable T-Scan examination results (3); and patients declining exam after enrollment (2). Table 4 below shows the distribution of select baseline characteristics by country.

Table 4. Select Baseline Characteristics (Specificity Arm) - (FDA Calculations).

Baseline Characteristics	**U.S.**	**Israel**	**Fisher's Exact-Probability**
Menopausal Status			
Pre-Menopausal	1228(98%)	490 (99%)	0.0161
Post-Menopausal	29 (2%)	3 (1%)	
Missing	1	0	
Hormone Usage			
No Hormones	745 (61%)	222 (50%)	0.000215
Hormones	482 (39%)	218 (50%)	
Missing	31	53	
Brassiere Cup Size			
A or B	570 (46%)	269 (57%)	0.00006302
C or More	673 (54%)	205 (43%)	
Missing	15	19	
First Degree Relatives with Breast Cancer			
No	1113(90%)	445 (93%)	0.0819
Yes	127 (10%)	36 (7%)	
Missing	18	12	
Race/Ethnicity			
Caucasian	866 (87%)	0	
Asian, American Indian, Black, or Hispanic	134 (13%)	0	
Missing	258	493	
Age			**t-test Probability**
Mean (SD)	34.6 (2.8)	34.2 (2.9)	0.0238
Range	30-39	30-39	

These data show statistically significant differences in the distribution of menopausal status, hormone use, bra cup size, and age between the US and Israel.

d. Results

Table 5 below shows the specificity results for U.S and Israel.

Table 5. Per Protocol Specificity (Specificity Arm) by Country (FDA Calculations)

Per Protocol Patient Population	**U.S.**	**Israel**	**Fisher's Exact-Probability**
Specificity	95.5% (1201/1258)	92.7% (457/493)	0.0241

One subgroup of cases excluded from the per protocol analysis, was that of women with an abnormal CBE (palpable mass). Fifty nine (59) non-evaluable patients with positive CBE were enrolled; the specificity of this patient group was 94.9% (see Table 6), very similar to the specificity found in the per protocol analysis (94.7%).

Table 6. Specificity (Specificity Arm) (Sponsor's Data)

Patient Population	**N**	**T-Scan Negative**	**Specificity**
Normal CBE (Per protocol)	1751	1658	94.7%
CBE positive	59	56	94.9%

The specificity results by covariates to contrast US and Israel are shown in Table 7.

Table 7. Per Protocol Specificity by Covariates (Specificity Arm - FDA analysis)

Baseline Characteristics	**US**	**Israel**	**Fisher's Exact-Probability**
Menopausal Status			
Pre-Menopausal	95%(1172/1228)	93%(454/490)	0.0240
Post-Menopausal	97%(28/29)	100%(3/3)	1.0000
Missing	1	0	
Hormone Usage			
No Hormones	95%(709/745)	94%(208/222)	0.3894
Hormones	96%(462/482)	92%(200/218)	0.0310
Missing	31	53	
Brassiere Cup Size			
A or B	97%(552/570)	97%(260/269)	0.8376
C or More	94%(635/673)	88%(181/205)	0.0048
Missing	15	19	

Baseline Characteristics	US	Israel	Fisher's Exact-Probability
First Degree Relatives with Breast Cancer			
No	95%(1057/1113)	93%(412/445)	0.0706
Yes	99%(126/127)	92%(33/36)	0.0341
Missing	18	12	
Race/Ethnicity			
Caucasian	96%(828/866)	0	
Asian, American Indian, Black, or Hispanic	91%(122/134)	0	
Missing	258	493	

The subgroups with statistically significantly greater specificity in the US than in Israel were premenopausal women, hormone use, large brassiere cup size (≥ C), and positive FHx of breast cancer. All other differences were not statistically significant or could not be done because of too much missing information (race/ethnicity).

e. Safety

There were no reported cardiac, neurological, dermal, thermal or allergic reactions or adverse events, nor any reports of patient discomfort. The sponsor states that this outcome echoed similar findings in the pilot study and in more than 10,000 prior examinations with the predecessor T-Scan™ 2000 device as reported in the previously approved PMA.

3. FDA's Further Discussion of the Specificity Arm:

In the Specificity Arm, the 59 women who had abnormal CBE were not included in the analysis as per protocol. However, the 163 women who had first degree relatives with breast cancer were included. It should be noted that the sponsor does not wish to indicate the device for women who have a positive family history. Table 8 shows certain differences in baseline characteristics in between Israel and US subjects noted during FDA's review.

Table 8. Comparison of Israel and US data in Specificity Arm (FDA Calculations)

Patient Characteristic	Israel	U.S.	Fisher's Exact-Probability
Ethnicity data missing	100% (493/493)	21% (258/1258)	<0.000000001
Bra cup size A or B	57% (269/474)	46% (570/1243)	0.00006302
Hormone usage	50% (218/440)	39% (482/1227)	0.000215

Race or ethnicity data was absent from the Israeli data and missing a fifth of the time from the US data. The difference is statistically significant. Israeli study participants also had statistically significantly smaller breasts and more hormone usage. FDA

believes that these characteristics are important influences on breast cancer risk and may also be important to interpreting specificity arm results for the US population.

4. Sensitivity (Biopsy) Arm

a. Introduction
The objective in this arm of the study was to evaluate the T-Scan's sensitivity for cancer. In addition, specificity for benign lesions was a secondary objective.

b. Study Design
FDA agreed to a sensitivity study partially enriched with older women in the age group 40-45. The basic eligibility criteria were as follows:

- Age 30-45, premenopausal
- Suspicious lesion on CBE, mammogram, ultrasound or MRI
- Referred and scheduled for breast biopsy

Patients were considered to have cancer only if there was histological confirmation of malignancy. Atypical hyperplasia and LCIS were considered benign.

The only differences in the inclusion criteria between the Sensitivity and the Specificity Arms of the study were that women between the ages of 40 and 45 were eligible to participate in the Sensitivity Arm but not in the Specificity Arm, and all women in the Sensitivity Arm were scheduled for breast biopsy. The exclusion criteria were identical between the two arms, except that women with palpable masses were excluded from the Specificity Arm, but included in the Sensitivity Arm. Women with positive FHx were included in both arms of the study.

The Sensitivity Arm consisted of 597 women enrolled at 6 clinical sites in Israel and 12 in the U.S. Of these subjects 414 were considered evaluable by FDA.

IMPORTANT NOTE TO PANEL MEMBERS: ***Because FDA has included 24 post-menopausal women (which include an additional 7 biopsy-positive cancer cases) in their per-protocol analysis, the results which appear in this memo differ slightly from those presented by the sponsor in their document***.
FDA has included postmenopausal cases in our analyses for several reasons:

1. They were not excluded per the original clinical protocol
2. The sponsor's proposed indications for use statement does not exclude post-menopausal women
3. Post-menopausal women were included in the Specificity arm study.

One hundred eighty- three (183) subjects were excluded from the analyses for the reasons below:

- Technical difficulties – T-Scan results available 66
- Technical difficulties – no T-Scan results available 4
- No biopsy results 44
- Declined exam after enrollment 4
- Exclusions based on eligibility 65

Of these 183 excluded patients, 37 subjects had cancer. The reasons for exclusion of the 37 cancer patients were as follows:

- "Technical" 19
- Age < 30 2
- Age > 45 11
- Prior Chemotherapy 4
- No T-Scan Result 1

Tables 9 and 10 below show the distribution of baseline characteristics for patients with T-Scan exams completed per protocol according to FDA's analysis. The results are based on per protocol cases separately presented for U.S. and Israel populations.

TABLE 9. Select Baseline Characteristics for *Benign* Cases (FDA Analysis)

Baseline Characteristic	**Israel (N=170)**		**U.S. (N=150)**		**Fisher's Exact Probability**
	N	**%**	**N**	**%**	
Age					
30-39	73	43%	76	51%	0.1790
40-45	97	57%	74	49%	
Mean (SD)	170	39.0 (4.3)	150	38.6 (4.2)	T-test probability 0.4371
Range	170	30 - 45	150	30 - 45	
CBE					
Normal CBE	92	54%	47	31%	0.00004598
Abnormal CBE	78	46%	103	69%	
Hormone Usage					
No Hormones	114	87%	125	86%	0.8614
Hormones	17	13%	21	14%	
Missing	39		4		
Menopausal Status					
Pre-Menopausal	160	98%	137	91%	0.0223
Post-Menopausal	4	2%	13	9%	
Missing	6		0		
Bra Cup Size					
A or B	58	40%	66	45%	0.4073
C or More	88	60%	80	55%	
Missing	24		4		
First Degree Relatives with Breast Cancer					
No	114	68%	101	68%	1.0000
Yes	54	32%	48	32%	
Missing	2		1		

Baseline Characteristic	Israel (N=170)		U.S. (N=150)		Fisher's Exact Probability
	N	%	N	%	
Size of Lesion (mm)					
≤18	93	73%	62	71%	0.7579
>18	34	27%	25	29%	
Missing	43		63		
Mean (SD)	127	14.7(8.5)	87	17.1(11.3)	T-test probability 0.4369
Range	127	5-50	87	3-76	
Race/Ethnicity					
Caucasian	0		56	40%	
Asian. American Indian, Black, Hispanic	0		83	60%	
Missing	170		11		

NOTE TO PANEL MEMBERS: ***FDA analysis (above and below) of lesion size uses an 18mm cut-off. The sponsor used 20mm in their report.***

These numbers show that there were statistically significantly more CBE normal and premenopausal women among benign cases in the Israeli sensitivity arm than among benign cases in the US sensitivity arm.

TABLE 10. Select Baseline Characteristics for *Malignant* Cases (FDA Analysis)

Baseline Characteristic	Israel (N=65)		US (N=29)		Fisher's Exact-Probability
	N	%	N	%	
Age					
30-39	26	40%	11	38%	1.0000
40-45	39	60%	18	62%	
Mean (Std)	65	39.8 (3.9)	29	39.9 (4.2)	T-test probability 0.9109
Range	65	30 - 45	29	30 - 45	
CBE					
Normal CBE	11	17%	7	24%	0.4103
Abnormal CBE	54	83%	22	76%	
Hormone Usage					
No Hormones	39	85%	23	85%	1.0000
Hormones	7	15%	4	15%	
Missing	19		2		

Baseline Characteristic	Israel (N=65)		US (N=29)		Fisher's Exact-Probability
	N	%	N	%	
Menopausal Status					
Pre-Menopausal	59	94%	26	90%	0.6743
Post-Menopausal	4	6%	3	10%	
Missing	2		0		
Bra Cup Size					
A or B	19	44%	12	48%	0.8046
C or More	24	56%	13	52%	
Missing	22		4		
First Degree Relatives with Breast Cancer					
No	40	68%	18	62%	0.6371
Yes	19	32%	11	38%	
Missing	6		0		
Race/Ethnicity					
Caucasian	0		14	48%	
Asian, American Indian, Black, Hispanic	0		15	52%	
Missing	65		0		
Size of Lesion (mm)					
≤18	32	55%	8	38%	0.2101
>18	26	45%	13	62%	
Missing	7		8		
Mean (SD)	65	22.3(16.1)	29	21.9(9.5)	T-test probability 0.8788
Range	65	5-80	29	9-44	

The FDA analysis shows that there were no statistically significant differences between Israel and the US for baseline characteristics among the malignant subjects, probably because of small group sizes.

Compared to the sponsor's benign subject group (see Sponsor's memo), the FDA benign subject group comprises a lower percentage of women with FH negative (68% vs 83%, Fisher's exact probability = 0.000025). Compared to the sponsor's cancer subject group, the FDA's cancer subject group comprises a lower percentage of women with FH negative (66% vs 84%, Fisher's exact probability = 0.008141). FDA thus believes that FHx is relevant to the interpretation of the Pivotal study results.

c. Results

Table 11 below shows the overall sensitivity results for all completed T-Scan exams (n=131) and the completed, per protocol, T-Scan exams (n=94) in women with pathology confirmed cancers, along with the sponsor's results.

Table 11. Overall sensitivity (Sponsor's and FDA's Analyses)

Patient Population	**N**	**T-Scan Positive**	**Sensitivity**
Per sponsor's protocol	87	23	26.4%
Per FDA protocol	94	24	25.5%
All data available	131	30	22.9%

The calculated sensitivities are quite similar. FDA continued with its definition of "per protocol" because important differences related to covariables emerged in later analyses, presented below and in the section on combining the results from the two arms.

Table 12 shows the specificity of T-Scan (regarding the benign cases as normal), by covariates and country. As can be seen, specificity did not vary between countries. The overall specificity = 80.6% (258/320) in the Sensitivity arm.

Table 12. Specificity by Covariates and Country for Benign Cases (Sensitivity Arm) (FDA Analysis)

Baseline Characteristic	**Israel (N=170)**		**US (N=150)**		**Fisher's Exact Probability**
	N	**%**	**N**	**%**	
Age					
30-39	73	88%	76	86%	0.8116
40-45	97	73%	74	78%	0.4771
CBE					
Normal CBE	92	78%	47	81%	0.8270
Abnormal CBE	78	81%	103	83%	0.8465
Hormone Usage					
No Hormones	114	82%	125	81%	1.0000
Hormones	17	82%	21	86%	1.0000
Missing	39		4		
Menopausal Status					
Pre-Menopausal	160	80%	137	82%	0.7683
Post-Menopausal	4	50%	13	85%	0.2189
Missing	6		0		

Baseline Characteristic	Israel (N=170)		US (N=150)		Fisher's Exact Probability
	N	%	N	%	
Bra Cup Size					
A or B	58	91%	66	88%	0.5711
C or More	88	73%	80	78%	0.5929
Missing	24		4		
First Degree Relatives with Breast Cancer					
No	114	79%	101	81%	0.7344
Yes	54	80%	48	83%	0.7996
Missing	2		1		
Race/Ethnicity					
Caucasian			56	86%	
Asian, American Indian, Black, Hispanic			83	81%	
Missing	170		11		
Size of Lesion (mm)					
=<18	93	73%	62	85%	0.0771
>18	34	85%	25	84%	1.0000
Missing	43		63		

Table 13 shows the sensitivity results by covariates and country.

Table 13. Sensitivity for Malignant Cases (Sensitivity Arm) (FDA analysis)

Baseline Characteristic	Israel (N=65)		US (N=29)		Fisher's Exact Probability
	N	%	N	%	
Age					
30-39	26	27%	11	0%	0.0797
40-45	39	36%	18	17%	0.2144
CBE					
Normal CBE	11	45%	7	0%	0.1013
Abnormal CBE	54	30%	22	14%	0.2419

Baseline Characteristic	Israel (N=65)		US (N=29)		Fisher's Exact Probability
	N	%	N	%	
Hormone Usage					
No Hormones	39	26%	23	9%	0.1820
Hormones	7	57%	4	0%	0.1939
Missing	19		2		
Menopausal Status					
Pre-Menopausal	59	32%	26	12%	0.0602
Post-Menopausal	4	25%	3	0%	1.0000
Missing	2		0		
Bra Cup Size					
A or B	19	21%	12	8%	0.6236
C or More	24	38%	13	8%	0.0655
Missing	22		4		
First Degree Relatives with Breast Cancer					
No	40	30%	18	6%	0.0464
Yes	19	37%	11	18%	0.4189
Missing	6		0		
Race/Ethnicity					
Caucasian			14	7%	
Asian, American Indian, Black, Hispanic			15	13%	
Missing	65		0		
Size of Lesion (mm)					
=<18	32	34%	8	13%	0.3955
>18	26	35%	13	15%	0.2760
Missing	7		8		

Sensitivity was statistically significantly higher in FH negative women in Israel. Other differences were not statistically significantly different, probably because of small subgroup sizes.

d. Safety

There were no reported adverse events, nor any reports of patient discomfort.

5. FDA's Discussion of the Sensitivity Arm:

A large amount of enrichment took place. Of those enrolled into the study and considered "evaluable", 55% (228/414) of the women were age 40-45. A significant number (57/94) of cancer cases (61% of total cancers) were from women age 40-45. The T-Scan sensitivity of 29.8% (17/57) in the 40-45 age group appears to have inflated the overall T-Scan sensitivity for all women with ages 30-45 to 25.5% (24/94), whereas the T-Scan sensitivity in women age 30-39, the intended use age group (but including CBE+ and FH+ cases), was only 18.9% (7/37).

In this study, 62% (257/414) of the women were CBE positive at baseline and 32% (132/405) were family history positive. When looking only at the patients with cancer, on which the Sensitivity results are based, 81% (76/94) had a positive CBE and 34% (30/88) were family history positive. Hormone usage was 15% (11/73) in the cancer patients and 14% (49/350) in the enrolled women with data. However, hormone status was missing in 22% (21/94) of the cancer patients and 15% (64/414) of the overall group.

The sponsor used Pearson's chi-square to examine the relationship between sensitivity and age, brassiere cup size, hormone use, family history of cancer, palpability of lesion, and cancer (lesion) size. There was no significant ($p > 0.10$) correlation between T-Scan results and the above covariables. However, for the *Specificity arm*, the sponsor used multiple logistic regression analysis to find that both bra size and age "showed significant independent effects ($p<0.001$ and $p<0.05$ respectively)", with specificity decreasing with both increasing bra size and increasing age. Therefore, FDA believes that any analysis of the probability of T-Scan 2000 detecting breast cancer should properly include statistically significant covariables such as bra size, country of origin and age, which the sponsor did not provide.

FDA compiled Table 14, showing the number of patients, cancer cases and detected cancer cases in target population age group of 30-39 and enriched age group 40-45.

Table 14. Results of Sensitivity Study in Target (30-39) and 40-45 Age Groups

Age Group	Total Number of Protocol Patients Evaluated	Number of Cancer cases	Number of Cancer Cases Detected	Number of Cancer Cases Detected with CBE Negative
30-39	186	37	7	1
40-45	228	57	17	4
30-45	414	94	24	5

As shown in the 5th column of the above table, the number of T-Scan detected cancers in the intended population is only 1.

Table 15 shows sensitivity by country.

Table 15. Sensitivity by Country

	U.S.	**Israel**	**Total**
Number of Cancer Cases	29	65	94
T-Scan Positive Cancer Cases	3	21	24
Sensitivity	10.3%	32.3%	25.5%

The sensitivity of the device in the U.S. population was 10.3% (Table 15), similar to the sensitivity reported in the pilot study with 61 cancers = 11.5% (7/61). It is unclear why the sensitivity in the Israeli population was statistically significantly higher with Fisher's Exact probability = 0.0386 and 95% CI = (3%; 40%).

6. Combined Results of the Two Arms of the Study

The sponsor calculated 'relative probability' (Pr) for breast cancer, defined as the probability that a woman who is T-Scan positive will have breast cancer relative to that of a woman randomly selected from the population at large. The following formula was used:

$$Pr = \frac{Se}{SeRca + (1-Sp)\,(1-Rca)}$$

In this formula, the relative probability (Pr) is a function of the sensitivity (Se), specificity (Sp), and the prevalence of cancer in the population (Rca).

On this basis, the sponsor states that device efficacy focused on T-Scan's capacity to identify risk that is equal to or greater than the risk detection standard provided by family history alone. The sponsor stated that to be considered efficacious, a positive T-Scan result would need to correlate with a breast cancer risk of $\geq$ 2.0 in the target population.

The sponsor combined its per protocol results from the two Arms of the study with the measured specificity of 94.7% (1658/1751), its measured sensitivity of 26.4% (23/87), and the estimated prevalence of carcinoma in women age 30-39 of 1.5/1000 women (Kerlikowske, 1993), to calculate the relative probability of a woman with a positive T-Scan examination having cancer to be 4.95 with a 95% confidence interval estimated by bootstrapping methods of 3.16 to 7.14. The sponsor's interpretation ist that, thus, a T-Scan positive woman is almost five times as likely as the average woman to have breast cancer. Thus, the T-Scan associated relative probability for breast cancer, as derived from the results of this study, significantly exceeds the threshold of 2.0, and thereby meets the primary study success criterion.

The sponsor also re-calculated with a sensitivity estimate of 18.9% (for ages 30-39) and obtained a relative probability of 3.6 with bootstrapped 95% CI of 1.43 to 6.19. FDA notes that the lower bound of this confidence interval does not exceed the threshold of 2.

The sponsor simulated the T-Scan intended use population by projecting the specificity arm results so that the overall cancer prevalence would be 1.5/1000, as shown in Table 16.

Table 16. Projected T-Scan study results to intended population (sponsor's analysis).

T-Scan	Normal	Benign	Malignant	Total
Negative	54,557 (94.7%)	245 (80.9%)	64 (73.6%)	54,866 (94.6%)
Positive	3053 (5.3%)	58 (19.1%)	23 (26.4%)	3,134 (5.4%)
Total	57610 (100%)	303 (100%)	87 (100%)	58,000 (100%)

The sponsor collapsed the normal and benign columns in Table 16 to create Table 17.

Table 17. T-Scan results in cancer and non-cancer cases (sponsor's analysis)

T-Scan	Non-cancer	Cancer	Total
Negative	54,802 (94.6%)	64 (73.6%)	54,866 (94.6%)
Positive	3111 (5.4%)	23 (26.4%)	3134 (5.4%)
Total	57,913 (100%)	87 (100%)	58,000 (100%)

The sponsor applied logistic regression to the data in Table 17 and reported a strong relationship between T-Scan results and presence of cancer, with adjusted odds ratio = 6.33 and 95% CI 3.93 - 10.21. The sponsor's model was used to derive the positive predictive value (probability of cancer if T-Scan is positive) of 0.00734, or 1 in 136. FDA notes that the odds ratio is actually crude because no covariables were in the model, and that basing the confidence interval on the projected numbers had very little impact on the width of the interval. FDA further notes that applying the crude odds ratio or logistic regression analysis to the basic table composed of the specificity data and the cancers from the sensitivity data yields an odds ratio of 6.4 (95% CI 3.8 – 10.8), basically the same as the one derived from Table 17.

The sponsor stated "Adjusting for some variability in prevalence, due to the potential claim that breast cancer in younger women may be under diagnosed, indicates that estimates of relative probability are little affected by a range of assumptions regarding the prevalence of cancer in the population. The prevalence of cancer in this intended use population has been reported to be 1-2 cancers/1000 women. Assuming a

prevalence of cancer of 1/1000 women, the estimated relative probability is 4.96. Assuming a prevalence of cancer of 2/1000 women would result in an estimated relative probability 4.94. If the relative probability is re-calculated using data exclusively from women under the age of 40 in the study, the relative probability based on the observed specificity arm results of 94.7% and the sensitivity arm results of 18.9% in women ages 30 to 39 was 3.6 with a bootstrapped 95% confidence interval of 1.43 – 6.19)."

7. FDA Discussion and Analysis of the Combined Results

a. FDA Calculations Using Sponsor's Method

FDA repeated the sponsor's calculation of relative probability using 94.6% specificity and 4 estimates of sensitivity:

- 25.9% used by sponsor, for all women 30-45, CBE+ and-, U.S. and Israel.
- 10.3%, as in all US data, including 40-45 year olds and CBE+.
- 2.7% for all women 30-39 who were CBE-, including Israel and U.S.
- 0% for women who were 30-39, CBE-, FH-, and in the U.S.

FDA also varied the assumed breast cancer prevalence rate in the calculations, and, like the sponsor, found that varying breast cancer prevalence while holding sensitivity constant did not change the relative probability. However, varying T-Scan sensitivity had a major impact; for sensitivity = 25.9%, the relative probability was 4.9, for sensitivity = 10.3%, relative probability was 2.0, for sensitivity = 2.7%, the relative probability was 0.53,and for sensitivity = 0%, the relative probability was 0. Note that the lower confidence bounds for the relative probability estimate of 2 falls below 2, so sensitivities of 10.3% and lower are not at least 2. Also note that any relative probabilities less than 1 show that T-Scan is worse than selecting patients at random for further breast cancer screening (random selection would have a ratio = 1).

Because of concern that covariables might confound the overall relative probability calculation, FDA applied SAS PROC LOGISTIC (Binary Logit Model) to the 2,165 per protocol women with both T-Scan results and:

- For the Specificity Arm, CBE negative (presumed normal) or
- For the Sensitivity Arm, biopsy results, with benign regarded as normal.

FDA found that Menopause (Post- vs. Premenopausal), Country (Israel vs. US), Family History (Yes vs. No), Hormone (Use vs. No use), and T-Scan (Positive vs. Negative) are each predictive for malignancy, as follows in Table 18:

Table 18. Results of FDA logistic regression analysis of results from both the Sensitivity and Specificity studies.

Effect	Estimated Adjusted Odds Ratio	Profile Likelihood 95% CI
Menopause	4.8	(1.7, 11.6)
Country	4.0	(2.4, 6.8)
Family History	3.6	(2.1, 5.9)
Hormone	3.3	(1.7, 6.7)
T-Scan	2.6	(1.3, 4.7)

Odds ratio results are practically equivalent to rate ratios in this instance because the prevalence of cancer is low. Hence, T-scan positive appears to have approximately the same effect as being post-menopausal, being in Israel, or having a family history of breast cancer, or not using hormones. Only being in Israel or having a family history meets the above criterion for the lower bound of the 95% CI of the relative breast cancer risk ≥ 2. Note that these logistic regression results are independent of the prevalence of breast cancer. They also show that controlling for the covariates is necessary for assessing the independent effect of T-Scan, and that the input of T-Scan was confounded by the covariables.

The sponsor's calculation method depends on T-Scan sensitivity. The Sensitivity Study results were obtained by applying T-Scan to patients already scheduled for biopsy. In other words, the normal step of mammographically (or otherwise) evaluating a T-Scan positive result in order to decide whether to schedule biopsy was not a factor in the Sensitivity Study, but would be a factor in clinical practice. Since the intermediate step is usually film mammography (recognizing that practice is not to depend on film mammography, and that practice is changing, for the sake of making the point here FDA will just discuss film mammography), the sensitivity of film mammography would have an important impact on the effectiveness of T-Scan.

b. FDA Benefit Risk Analysis

FDA conducted a Benefit Risk Analyses modeled on the method used by Feig. This method depends on breast cancer prevalence, and mammographic sensitivity as well as T-Scan sensitivity because the risks of mammography are included in the model. The choice of estimates for each variable is explained below.

The estimate of breast cancer prevalence used by the sponsor was for women attending breast cancer screening clinics and would not apply to women age 30-39 attending a regular annual physical examination, which is the "presenting prevalence" for T-Scan. To calculate that prevalence, FDA first considered the prevalence of breast cancer in all women attending their routine annual physical examination, using national Surveillance, Epidemiology, and End Results (SEER) data generated by the National Cancer Institute.

In the steady state (once T-Scan has been in use for some time), women will have their first T-Scan screen at age 30, when prevalence would be approximately 3 times the incidence, 0.0006. For each annual examination after age 30, incidence is believed to be the appropriate measure because it measures the accumulated new

cases since the last visit. FDA used simple interpolation to calculate the yearly incidence rates. Using the rate for age 40-44 to interpolate rates at ages 36 through 39 accounted for the slight increase in the rate for 40-44 above the plotted curve for all adult women. The resulting estimated average presenting prevalence rate for ages 30-39 is 0.00058.

The above calculations are for all women age 30-39. However, the population of interest is women of that age who are also FH- and CBE-. FDA's estimation of the prevalence of breast cancer among the intended use population required knowledge of the proportion of such women who are FH-, the proportion of them who are CBE-, and the reduction in prevalence associated with FH- and CBE-. In the absence of contrary evidence, FDA assumed that CBE status is independent of FH status.

For FH, FDA used data from the recent meta-analysis of 52 studies (Collaborative Group on Hormonal Factors in Breast Cancer), which showed that the proportion of women age <40 who are FH+ is approximately 0.04 and that the relative risk (RR) of cancer among those women is approximately 3. This RR estimate is higher than the one selected by the sponsor from the same study because the FDA used the age-specific estimate and the sponsor used the all-ages estimate.

The only study FDA found of the CBE+ rate was by Bobo et al. Their observed CBE+ rate was higher among 30-39 year olds than 40-49 year olds. Since the 30-39 year old population may have been biased towards concerned women who came in because of symptoms, FDA used the 40-49 year old estimates of 8.7% of women being CBE+, and the RR of cancer among CBE+ compared to CBE- women is 25. FDA then used arithmetic to estimate that out of a million women age 30-39, 876,480 women would be both FH- and CBE-, and their presenting breast cancer rate would be 0.000174. Since these estimates would be unfavorable to the sponsor, and might be biased, FDA also selected 2 other sets of assumptions: CBE+ rate of 3% and breast cancer RR for CBE+ of 10 or 3. The assumption of 3% prevalence of CBE led to an estimate of 931,200 women being both CBE- and FH-. Assuming that RR = 10 led to an estimate that the breast cancer prevalence is 0.000423, and assuming that the RR = 3 led to an estimate that the breast cancer prevalence is 0.000507. Therefore, depending on assumptions, the presenting prevalence among age 30-39 women who are both FH- and CBE- might range from 0.00017 to 0.00051.

FDA used 2 estimates of mammography sensitivity. One choice was the estimate proposed by the sponsor, 70%. A second choice was based on the estimate reported by Pisano for film mammography, 50%, for women age 40-49. The FDA view is that the Pisano sensitivity is so low because digital performed better than film in women of that age, and identified many more cancers than would be identified in a film-only setting. To adjust the Pisano sensitivity estimate for age 30-39, FDA considered evidence in reports referenced by the sponsor, and concluded:

- Mammography sensitivity decreases with greater mammographic density (Carney, Kerlikowske 1996, Kolb, Pisano, Poplack, Smith-Bindman) and mammographic density increases for younger age (Carney, Kerlikowske 1996, Stomper).

- Mammographic sensitivity is lower for pre- than postmenopausal women (Kerlikowske 1996, Kolb, Pisano) and women in their 30s are more likely to be pre-menopausal than women in their 40s.
- Mammography sensitivity decreases with lower age (Carney, Kerlikowske 1996, Kerlikowske 2000, Kolb, Pisano, Smith-Bindman).

Mammography sensitivity in women in their 30s is difficult to establish because women at that age are not generally subject to screening. However, the data for mammographic densities and menopausal status lead to the reasonable conclusion that mammographic sensitivity is, indeed, lower for women in their 30s than women in their 40s. The range of decreases in mammographic sensitivity comparing women in their 40s to women in their 30s was reported in just a few studies, and ranged from -3% to 16%. To be conservative, FDA selected a 5% reduction from the Pisano estimate of 50%.

In the paper by Feig et al, Table 3 showed the benefits and risks from annual screening mammography of 1 million women age 40-74: 18,900 lives would be saved due to screening, versus 21.6 deaths caused, for a benefit/risk ratio of 875/1 and net benefit in lives of 18,878. FDA performed similar calculations for age 30-39, only substituting "cancers detected" for "lives saved." FDA modified the mammographic dose per image used by Feig from 2 to 1.6 mSv per view based on published data (Suleiman) and lifetime radiation risk for women in their 30s according to BEIR V, to calculate 14 deaths per million screens.

The following table shows benefit and risk calculations using different combinations of breast cancer presenting prevalence, T-Scan sensitivity, and mammogram sensitivity.

Table 19. Net benefit (cancers detected minus possible deaths caused) of one T-Scan screen of each of 1 million women age 30-39 who are FH- and CBE-.

			Mammogram sensitivity			
			70%		**45%**	
Presenting prevalence	**T-Scan sensitivity**	**Possible deaths caused**	**Cancers detected**	**Net benefit**	**Cancers detected**	**Net benefit**
0.00150	25.9%	3.6	272.0	268.3	174.8	171.2
0.00150	10.3%	1.4	108.2	106.7	69.5	68.0
0.00150	2.7%	0.3	28.4	27.9	18.2	17.8
0.00051	25.9%	3.6	92.5	88.8	59.4	55.8
0.00051	10.3%	1.4	36.8	35.3	23.6	22.2
0.00051	2.7%	0.3	9.6	9.3	6.2	5.8
0.00017	25.9%	3.6	30.8	27.2	19.8	16.1
0.00017	10.3%	1.4	12.3	10.8	7.9	6.4
0.00017	2.7%	0.3	3.2	2.8	2.1	1.6

These calculations show that when the risk of mammography is accounted for, the relative benefit of T-Scan is highly dependent on uncertain factors:

- The true sensitivity of T-Scan in the intended use population, which is related to age, menopausal status, family history, and country.
- The presenting prevalence of breast cancer in the intended use population, which depends on the proportion of women with CBE+ (not well documented) and the increased risk due to CBE+ (not well documented), the proportion of women with FH+ (well known) and the increased risk due to FH+ (well known), as well as the dependence of CBE+ on FH+ (not well documented).
- Mammographic sensitivity in the intended use population (not well documented).

For the intended use group (age 30-39, FH-, CBE-) with T-Scan sensitivity = 0%, there is no calculated benefit.

V. Supplemental Clinical Studies

The sponsor has included several clinical references in their PMA submission in which their device is studied for a similar indication. These are summarized here. However, it should be recognized that FDA did not have access to the line data for these references and was able to comment only on the articles provided. Therefore, an in-depth review of these studies was not possible.

A. Journal Article: Prospective study of electrical impedance scanning for identifying young women at risk for breast cancer (Stojadinovic et al., Breast Cancer Research and Treatment, 2006)

This study closely resembles the current PMA submission but with different numbers of patients, again using a two- armed data collection approach. A total of 1361 patients were in the specificity arm with 67 having positive TS-Scan exams and a total of 189 patients were in the sensitivity arm with 50 having cancer and T-Scan ED correctly identifying 19. This produces a Sp=95.1% (1294/1361) [CI: 94.0-96.2%] and Se=38% (19/50) [CI: 24-49%]. The sensitivity was 29% and 42% for women 30-39 years of age and 40-45 years of age, respectively. The study did not distinguish between patients who were CBE negative and FH negative when reporting results. In addition, many of the clinical sites are the same as the ones used for data collection in this PMA. It would appear that much of the data used for the manuscript overlaps with the data submitted in this PMA application. The general conclusions in the manuscript are similar to the conclusions being drawn by the sponsor in this application and many of the same issues expressed in this review apply to the manuscript results as well.

B. Journal Article: Electrical Impedance Scanning for the Early Detection of Breast Cancer in Young Women: Preliminary Results of a Multicenter Prospective Clinical Trial, (Stojadinovic et al., Journal of Clinical Oncology, 2005)

The sponsor also submitted this publication in support of their PMA. It should be noted that FDA has not been given access to the line data and therefore cannot confirm any results presented in this study. The study enrolled 1,103 women undergoing screening CBE, imaging or biopsy. This included 579 US subjects at 3

sites and 524 Israeli subjects at 3 sites. Baseline demographics for the subjects who were age < 40 (N=580) were as follows:

- Pre-menopausal 556 (95.7%)
- FH Negative 454 (78.3%)
- CBE Negative 437 (75.5%)

The sponsor calculated the sensitivities as:

- Overall (all ages and sites) 5/29 17.4% (4%; 30%)
- Age < 40 3/6 50.0%

It should be noted that there were some differences in the cancers which T-Scan picked up versus missed as illustrated below:

	T-Scan Pos (n=5)	T-Scan Neg (n=24)
Mean age	41.2	53.0 ($p<0.05$)
% Palpable	60%	29%
Mean tumor size	1.7 cm	1.7 cm
Mean BIRADS	4.0	3.8
% BIRADS 4/5	60%	79%

The reference speaks to Specificity:

- Overall 89%
- Age < 40 89%

Note that the Specificity, which was calculated in the same population as the Sensitivity, is lower than that in the Specificity arm of the pivotal PMA study (95%).

The authors then calculate the relative risk:

- Overall 1.53 (Se 17%, Sp 89%, Prevalence 6/1000)
- Age < 40 4.52 (Se 50%, Sp 89%, Prevalence 1.5/1000**)**

Without access to the line data, it is difficult for FDA to fully interpret these results.

C. Annual Report for Electrical Impedance Scanning (EIS) for the Early Detection of Breast Cancer (W81XWH-05-2-0011)

This is a five center, U.S. military, prospective study of woman aged 30-45 years who undergo annual physical cancer screening examinations. Participants underwent clinical breast exam (CBE) followed by EIS using the T-Scan. Woman who were positive on the T-Scan were referred for further breast imaging and biopsy, if indicated, along with women identified as having suspicious finding by other means.

Year 1 of this trial has been completed and the sponsor has submitted the Annual Report from this study as an amendment to their PMA submission. As of December 31, 2005, there were a total of 1393 women enrolled in the study with a diversity of ethnic backgrounds representing the U.S. military population in this age range.

FDA was not provided access to the line data for this supplemental data set.

Table 20 summarizes the follow-up results based on age and T-Scan outcome. Table 21 summarizes the T-Scan performance by age group and provides estimates of sensitivity and specificity for each age group. It is simply a reformatting of the data presented in Table 11 of the Annual Report. Note, the Ca+ category includes both high-risk and cancer diagnosis and that no Ca+ patients have, at this point, been identified in the 30-39 age range.

Table 20. Results from follow-up by T-Scan outcome and age (author's table).

Scan	Age	Total	US	(Susp.)	MX	(Susp.)	MR	(Susp.)	BX	(HR, Ca)
TS+ *	<40	49	8	0	37	0	32	0	0	0
	40+	49	4	0	46	0	32	2	3	1
TS-	<40	747	47	4	82	4	17	0	5	0
	40+	540	62	6	378	7	21	2	13	2

*TS: T-Scan, US: ultrasound, MX: mammography, MR: magnetic resonance, BX: biopsy, Susp: suspicious, HR: high risk, Ca: cancer.

Table 21. T-Scan ED performance by age group (author's table with FDA calculations).

	Age 30-39			Age 40-45			Total		
	Ca+	Ca-	Total	Ca+	Ca-	Total	Ca+	Ca-	Total
TS+ *	0	49	49	1	48	49	1	97	98
TS-	0	747	747	2	538	540	2	1285	1287
TS+ rate	0.06			0.08			0.07		
Se	0.0			0.33			0.33		
Sp	1.0			0.92			0.93		
PPV	0.0			0.02			0.10		
Ca rate	0.0			0.005			0.002		

*Ca: cancer, TS: T-Scan, Se: sensitivity, Sp: specificity, PPV: positive predictive value.

The authors conclude from this study that their interim results are consistent with an earlier validation study of 2,035 young women undergoing CBE and T-Scan exams by showing that T-Scan positive woman is more than six times as likely as the average woman to have breast cancer.

The Annual Report does not define high-risk patients and does not indicate if the single TP was a high-risk or actual cancer patient.

The sensitivity calculation was based on the identification of 1 of 3 high-risk, cancer patients in the 40-45 age range. No patients with cancer were identified in the 30-39

age range. Error bars were not reported but would be expected to be large with only three total TPs.

No CBE or FH results are reported so it is unknown whether or not the T-Scan detected the lesion from a patient with a negative CBE and negative family history, the intended use characteristics.

It appears that the author's argument for the overall benefit of T-Scan is based on the 40-45 year old women but extended to the 30-39 women and is based on mean performance without considering confidence intervals.

The reported specificity of 0.930 falls outside the reported 95% CI of 0.939 – 0.959 for the PMA Pivotal Study (see Table 3).

VI. FDA Comments on Potential Post-Approval Study.

NOTE TO PANELISTS: ***FDA's inclusion of a section/discussion on a Post-Approval study in this memo should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for pre-market approval and a recommendation from the Panel on whether to approve a device or not must be based on the premarket data. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding a potential post-approval study should the panel find the device approvable following its discussions and deliberations of the pre-market data.***

In the case of a tool to screen for a rare disease, the correct study (to estimate sensitivity, specificity, and positive predictive value in the same study group) is quite burdensome because of the large study size required. CDRH therefore allowed, pre-market:

- 2 study groups to separately estimate specificity and sensitivity for the intended use population.
- The sensitivity study group enrichment with cases.
- To maintain reasonable assurance of validity, the case mix must represent the case mix in the intended use population.

However, in this case, the pre-market study used an enriched population in the sensitivity study, and this population was not identical to the intended use group. A post-approval study should not be used to:

- establish (rather than verify) the actual sensitivity of a device.
- provide reasonable assurance that benefit will definitely exceed risk in the absence of such assurance from the pre-market study.

If the panel recommends that this PMA be approved, FDA will ask the panel to make recommendations on the need for and design of an appropriate post-approval study (PAS). FDA believes that the PAS should be large enough and of sufficient power to demonstrate reliably the sensitivity, specificity, and positive predictive value of T-Scan in the intended use U.S. population and that these 3 parameters should be measured in the same study population. FDA suggests that the study be designed to demonstrate that the rate of cancer detection attributable to T-Scan is statistically significantly higher than the comparable rate among women in the intended use population who do not obtain T-Scan screens. FDA believes that it would be appropriate for the comparison group to be contemporaneous because breast cancer screening practice is evolving. The study must include prevalent and incident cases. For all T-Scan positive screens, immediately subsequent screens and diagnostic procedures should be reported (for example, number of mammographic views, type and numbers of biopsies, etc.). FDA believes that the following covariates should be assessed in any such PAS:

- age;
- menopausal status;
- hormone use, contraceptive or replacement;
- date of last menstrual period and usual length of menstrual cycle, to estimate stage of monthly breast tissue proliferation or reduction;
- brassiere cup size;
- race/ethnicity;
- breast cancer gene status, if known; and
- history of T-Scan use, other breast screens (e.g., CBE, digital or film mammography), and breast diagnostic procedures (e.g., digital or film mammography, ultrasound, biopsy), and the results of each.

FDA suggests that other outcomes should be measured including:

- T-Scan refusal among women who were offered T-Scan; and,
- for T-Scan positive screens that result in no finding of breast cancer, subsequent use of T-Scan or other breast screens.

In addition, FDA would recommend that the sponsor consider measuring differences in cancer stage at detection and ultimate breast cancer mortality.

VII. References

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