Mirabel Medical Systems, Inc.
T-Scan 2000 ED, PMA P050003 Panel Pack
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PANEL PACK
EXECUTIVE SUMMARY

T-SCAN 2000 ED
P050003
MIRABEL MEDICAL SYSTEMS, INC.

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1.0 OVERVIEW OF PRODUCT CONCEPT

T-Scan™ 2000 ED (T-Scan ED) is a noninvasive and radiation-free device for breast cancer risk detection in asymptomatic women who are younger (30 to 39 years of age) than the recommended minimum age for screening mammography. The device detects electrical impedance changes in breast tissue that are associated with an increased risk of breast cancer. A positive T-Scan ED 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.

> **The T-Scan exam is incorporated into the annual or routine well-woman visit and is a complement to the current Standard of Care, the Clinical Breast Exam (CBE) for asymptomatic women under 40. Only women who have a normal CBE and who are not at increased risk for breast cancer for other reasons (for example, family history) are offered the T-Scan ED exam. It is not a diagnostic test for breast cancer, and is not a replacement for mammography.**

The pivotal study of the T-Scan ED determined that a positive result reflects a relative risk for breast cancer 4.95 times higher than the average risk, and higher than the standard at which mammography is currently recommended for those over 40. **Table 1** (below) provides a list of risk factors commonly used for considering mammography screening for women under 40, and the relative risk for breast cancer associated with each.

While breast cancer risk is comparatively lower in younger women than it is in older women, the disease is a very significant health concern in women of all ages. Breast cancer is the principal cause of cancer death for women age 15-54 (ACS 2003). Some 12,000 women under age 40 will be diagnosed with breast cancer this year (NCI 2004).

Only a small minority of women who develop breast cancer carry a known risk factor. According to most studies, only about 10% of women who develop breast cancer have a documented family history of the disease or a genetic predisposition for it. Thus, 90% of women who develop breast cancer do not have a known risk factor and, because of the limitations of the CBE, approximately 71% of cancers in women under age 45 are identified by self-detection (Coates *et al.* 2001).

The T-Scan ED offers an additional means by which to identify young women who are at increased risk for breast cancer, and thereby provides an important opportunity to offer increased surveillance and screening.

Table 1

RISK FACTORS AND LIFETIME RELATIVE RISK OF BREAST CANCER USED TO RECOMMEND IMAGING/SCREENING BEFORE AGE 40

Risk Factor	Condition	Relative Risk	Reference
Family History	One 1st degree relative	1.7-2.0	Pharoah *et al.* 2000; Collaborative Group on Hormonal Factors in Breast Cancer 2001
	Two 1st degree relatives	2.92	Collaborative Group on Hormonal Factors in Breast Cancer 2001
	Three or more 1st degree relatives	3.9	Collaborative Group on Hormonal Factors in Breast Cancer 2001
Genetic Factors	BRCA1	5.7	Schwab *et al*. 2002
	BRCA2	5.7	Schwab *et al*. 2002
Histological results of breast biopsy	Previous Breast Cancer	2.0-4.0	Feig *et al*. 1998
	Atypical Hyperplasia	4.0	Feig *et al*. 1998
	LCIS	5.9-12.0	Feig *et al*. 1998
Electrical Impedance	**Positive T-Scan ED**	**4.95**	**Pivotal Trial (Mirabel Medical Systems)**
Electrical Impedance	**Positive T-Scan ED**	**6.00**	**Department of Defense, Annual Report: Electrical Impedance Scanning (EIS) for the Early Detection of Breast Cancer in Young Women 2005**

The T-Scan ED breast cancer risk assessment paradigm is similar to other risk assessment methods approved by FDA that identify patients who require additional surveillance despite the fact that age alone would not qualify them for routine screening. The most similar risk assessment model in the field of obstetrics and gynecology is the quadruple or nuchal translucency tests for Down's Syndrome.

Like the risk for breast cancer, the risk for Down's Syndrome increases with age. Thus, screening guidelines suggest that women who become pregnant at age 35 or older consider amniocentesis or chorionic villus sampling (CVS) to screen for Down's Syndrome. The evolution of the quadruple test and nuchal translucency measurement allows for noninvasive and inexpensive risk assessment of women under the age of 35. This test identifies women who are at elevated risk and thus likely to benefit from more intensive screening that is recommended for women above the age of 35.

Similarly, the T-Scan ED exam utilizes Electrical Impedance Sampling (EIS) of breast tissue in order to identify women under age 40 who are at a level of risk that justifies the consideration of additional screening.

2.0 SUMMARY OF PRODUCT INFORMATION AND DATA

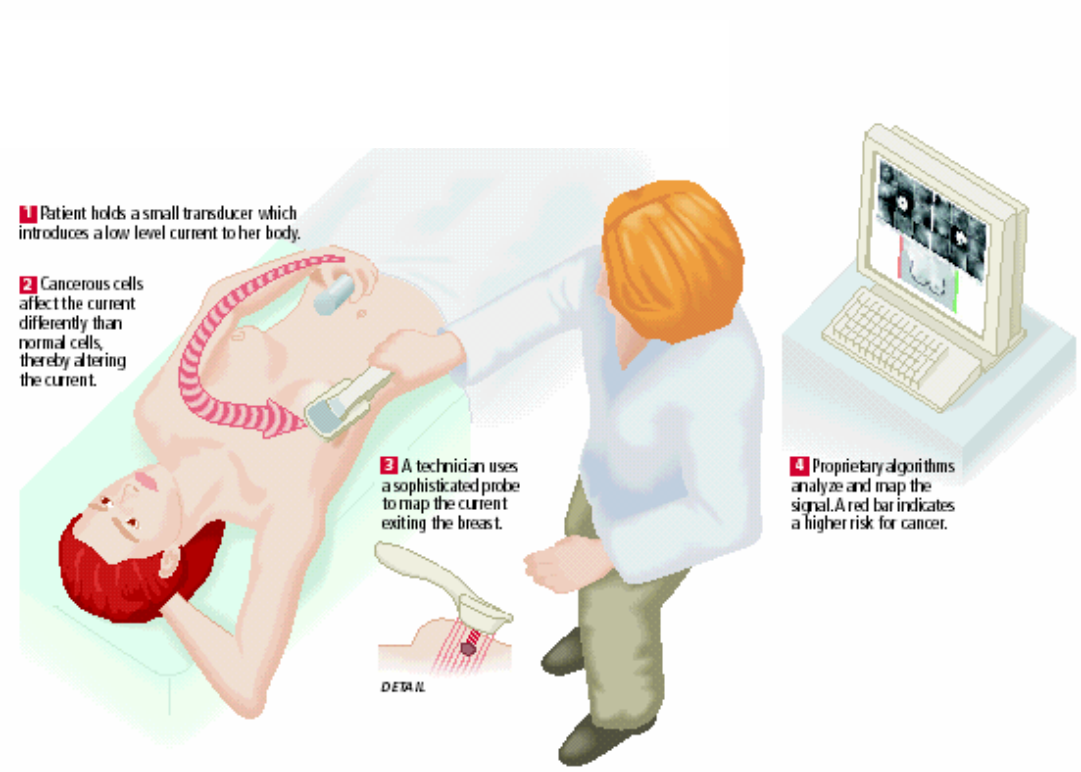
2.1 PRODUCT DESCRIPTION

T-Scan ED is a noninvasive and radiation-free device for breast cancer risk assessment using electrical impedance sampling (EIS). The system is intended for use as a complement to clinical breast examination (CBE) in asymptomatic women who are younger than the recommended minimum age for annual screening mammography (age 40). During the 6-minute exam, impedance measurements are analyzed in real time by the EISYS™ algorithm which has been trained to discriminate between normal and abnormal impedance parameters and objectively indicate to the examiner if the exam result is normal or suspicious. When used in combination with CBE, the T-Scan helps identify young women who are at increased risk for breast cancer but who would be overlooked by the current Standard of Care using CBE and family history alone. A positive T-Scan ED result provides physicians with additional information to guide a recommendation regarding further breast examination, *e.g.*, mammography or ultrasound.

Figure 1 below is an illustration of the EIS breast cancer risk assessment exam.

Figure 1

T-Scan 2000 ED Examination



2.2 PROPOSED INDICATIONS FOR USE

The T-Scan ED is indicated for use as a complement to CBE in asymptomatic women who are 30 to 39 years of age with a negative CBE 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.

2.3 UNMET CLINICAL NEED

Breast cancer is the leading cause of cancer death for women between the age of 15 and 54, accounting for more than 12,000 new cases in women under 40 each year (ACS 2003). One (1) in 229 women will be diagnosed with breast cancer by age 40 (NCI 2004). Thus, while breast cancer is less common in young women than it is in older women, it remains a very significant health concern for young women as well. However, current guidelines do not recommend annual screening mammography for average-risk women below the age of 40 because the lower incidence of breast cancer in younger

women, combined with a sensitivity for cancer detection that is 10-15% lower in premenopausal women, is not considered cost effective.

The Standard of Care for screening average-risk women under the age of 40 is CBE only, supported by monthly breast self-examination (BSE). The CBE is considered insufficient because it is highly subjective, difficult to compare from year to year, and has been shown to have very limited sensitivity for small cancers (Kriege *et al*. 2004). Because the CBE is less sensitive for small lesions, most cancers discovered in this manner have been growing for approximately six years (Kopans 2000). A concrete indication that CBE alone is ineffectual for screening young women comes from a Centers for Disease Control (CDC) report showing that 71% of cancers in women under age 45 are self detected (Coates *et al.* 2001).

A delay in detection of cancer from the inadequate screening of younger women is associated with poorer survival, more invasive and expensive treatment regimens, and increased morbidity. The need for earlier detection in younger women is especially relevant because breast cancer in younger women tends to be more aggressive than in older women (Fisher *et al.* 1997; Kopans 1998; Xiong *et al.* 2001; Dubsky *et al.* 2002; Love *et al.* 2002).

There is an important clinical need for a modality with which to address the absence of a breast cancer screening paradigm for women below the age at which screening mammography is initiated.

2.4 DEVELOPMENT OF T-SCAN ED

The association between particular electrical impedance parameters and malignant cells has been recognized and published as early as 1926 (Fricke and Morse 1926). However, the large volume of impedance data and the complex calculations required for the discrimination between benign and malignant cells prevented this technology from becoming clinically useful until the advent of improved computerized platforms. In 1995 Mirabel Medical Systems (then TransScan Medical) began developing the first clinically efficacious device to detect malignant breast lesions.

Following a clinical study conducted largely in Israel and Europe, the U.S. FDA approved Mirabel's first system, the T-Scan 2000, identifying it as a "major medical device breakthrough." The initial device was approved for use as "an adjunct to mammography in patients who have equivocal mammographic findings within ACR BI-RADS™ categories 3 or 4. In particular, it [was] not intended for use in cases with clear mammographic or non-mammographic indications for biopsy. This device provide[d] the radiologist with additional information to guide a biopsy recommendation."

Since that time, Mirabel has focused on refining the technology to address the unmet clinical need discussed above: the identification of young women (under 40) who are at

increased risk for breast cancer and should be considered for increased surveillance, monitoring and imaging.

EIS is not an imaging system as are other technologies such as ultrasound, mammography and MRI. The T-Scan 2000 ED analyzes a series of approximately 40,000 measurements relating to the impedance properties of the breast. By measuring conductance and capacitance across the breast, the system identifies breast changes associated with malignancy. 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.

The T-Scan ED, subject of the current PMA, is a modified version of the original T-Scan 2000 using the same measurement technique, patient interface and electrical current levels, but incorporating a software post processing algorithm. Thus, the T-Scan ED offers a ratio of sensitivity and specificity designed to be consistent with a risk assessment tool – as opposed to the very high sensitivity and moderate specificity of the prior T-Scan 2000 – which is a diagnostic tool.

2.5 PIVOTAL STUDY

A pivotal study was designed with input from FDA to determine the ability of the T-Scan ED to identify patients with *at least* a 2-fold increased relative risk for breast cancer in the target population (asymptomatic, otherwise average-risk women aged 30-39). The current Standard of Care identifies women with a relative risk of 2.0 or more to be "at risk". These women are offered additional imaging, greater surveillance and enrollment in specific management protocols (**Table 1**; and Kramer and Brown 2004; Pharoah *et al.* 2000; Tilanus-Lindhorst *et al.* 2000). Based on this standard, Mirabel proposed to FDA that a positive T-Scan ED result would need to reflect a relative risk of 2.0 or more to be clinically useful. This value was accepted by FDA as the "success threshold" prior to initiation of the pivotal study.

The safety of the device has been previously established as part of the initial PMA (P970033) and was confirmed in this trial.

Study Design

The clinical study was designed as a two-arm trial, where one arm estimated specificity (the false positive rate) and the other arm estimated sensitivity (cancer detection rate). As discussed above, the primary endpoint, relative probability of breast cancer, is a function of the estimated rates determined by both arms: sensitivity, specificity, and the prevalence of cancer in the population.

From a purely statistical perspective, the baseline assumption is that if a risk assessment tool has a specificity of 90%, about 10% of subjects would test positive. If the sensitivity

is 20%, then 20% of cancers would be identified among the 10% of subjects who tested positive. This "screen positive" cohort would equate to a relative probability of 2.0 of being at risk of cancer compared to the population at large.

Specificity Arm

The primary objective of the Specificity Arm of the study was to determine specificity in a cohort of women who were representative of the intended use population. Women were enrolled at 17 clinical sites in the U.S. and Israel who had a negative CBE and met all other inclusion and exclusion criteria.

Once enrolled, all patients had a CBE by a qualified examiner (typically the referring physician or the principal investigator). Women were also questioned regarding potential covariates such as hormone use, brassiere size and family history of breast cancer. It was assumed that all women in the Specificity Arm of the study were free of breast cancer. Finally, women in this arm had an EIS examination using the T-Scan ED.

Sensitivity Arm

The primary objective in this arm of the study was to calculate the sensitivity of the T-Scan ED to detect breast cancer. In addition, specificity for benign lesions was a secondary objective. Unlike the Specificity Arm that was confined to the intended use population (*i.e.*, women age 30-39 without a palpable mass), in designing the Sensitivity Arm, it was impractical to limit the study subjects to the intended use population because the relatively low incidence of breast cancer in this age group and the fact that the majority of cancers detected in this age group are palpable at the time of detection would limit accrual of a sufficient sample. A design was developed with FDA and agreed upon in advance of the study to enrich the population in two ways:

(1) Women in the Sensitivity Arm were between the ages of 30-45 as opposed to 30-39 in the Specificity Arm. However, only pre-menopausal women in this age range were included as subjects; and

(2) Women in the Sensitivity Arm were awaiting biopsy based on a prior finding (abnormal mammogram, palpable mass, etc.).

Thus, in order to identify a cohort of biopsy-positive women (*i.e.*, the cohort ideally suited to calculate sensitivity), this study required the screening of women who were undergoing biopsy due to earlier positive screening. This cohort does not represent the group of women who are proposed for T-Scan screening (average risk women 30-39 with negative CBE). The goal of this arm was to obtain a measurement of sensitivity to utilize in the formula to calculate relative probability, the primary variable.

Women were enrolled at 18 clinical sites in Israel and the U.S. who had a suspicious breast lesion based on results of a CBE, mammography, ultrasound or MRI, had been scheduled for breast biopsy, and met all other inclusion and exclusion criteria. Once

enrolled, all patients had a CBE by a qualified examiner (typically the referring physician or the principal investigator). Specific attention was paid to the CBE and the presence or absence of a palpable breast mass. Women were also questioned regarding potential covariates such as hormone use, brassiere size and family history of breast cancer. Finally, women in this arm had an EIS examination using the T-Scan ED prior to their biopsy procedure.[1]

Women were considered positive for breast cancer only if they had histological confirmation of malignancy. Histological diagnosis was performed by experienced breast pathologists. For the purposes of this study, atypical hyperplasia and lobular carcinoma in situ (LCIS) were regarded as a benign finding, and not a malignant lesion. Ductal carcinoma in situ (DCIS) was classified as a malignant lesion.

Study Results

Specificity Arm

Of the 1946 women enrolled, 1935 T-Scan ED examinations were completed, of which 1751 were completed per protocol. Exams or subjects were excluded from the per protocol analysis based on: patients not meeting the eligibility criteria (179); technical difficulties during the T-Scan ED examination (18); and patients declining an exam after enrollment (2).

The overall specificity results for all completed T-Scan ED exams was 94.5% and for the per protocol T-Scan ED exams was 94.7%. The specificity was unaffected by the presence of a palpable mass, menopausal status, hormone use, or family history of breast cancer. It was significantly related to brassiere cup size, being lower (although still above 90%) for larger-breasted women.

Of the cases excluded from the per protocol analysis, perhaps the most important subgroup is that of women with an abnormal CBE (palpable mass). Specificity for women with normal CBE was 94.7% and for those with abnormal CBE was 94.9%. While this subgroup is not clinically relevant to the target population, since women with a palpable mass are not indicated for a T-Scan ED, it is nevertheless relevant to the interpretation of data in the Sensitivity Arm of this study (see below) where a large proportion of women had palpable lesions.

Importantly, there were no reported cardiac, neurological, dermal, thermal or allergic reactions or serious adverse events. The safety profile 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 application.

[1] More women consented to a T-Scan ED exam prior to their biopsy at sites in Israel than in the U.S. Consequently, the trial had more cancer patients in Israel than in the U.S.

Sensitivity Arm

Of the 597 women enrolled, 545 completed T-Scan ED exams and biopsies, of which 390 had exams completed per protocol (303 benign cases; 87 cancer cases). Exams were excluded from the per protocol analysis based on patients not meeting the eligibility criteria (89), no biopsy results (44), technical difficulties during the T-Scan ED examination (70), and patients declining the exam after enrollment (4).

The overall sensitivity results for all completed T-Scan ED exams was 22.9% and the sensitivity for the completed, per protocol, T-Scan ED exams was 26.4% in women with pathology-confirmed cancers.

Importantly, there was no significant ($p > 0.10$) correlation between EIS results and categorizations of patient age, brassiere cup size, hormone use, family history of cancer, palpability of lesion and cancer (lesion) size.

Despite the statistically non-significant correlation of T-Scan ED result with lesion size, results from this study were consistent with several prior EIS studies indicating that EIS technology is particularly proficient in the detection of smaller lesions (≤ 2cm) (Fuchsjaeger *et al.* 2002a; Fuchsjaeger *et al*. 2002b; Wersebe *et al*. 2002). In this study, sensitivity for smaller lesions (≤ 2cm) was 35.6% as compared with a sensitivity of 22.2% for larger lesions (> 2cm).

There were no reported cardiac, neurological, dermal, thermal, allergic reactions or serious adverse events. This result confirmed similar findings in the pilot study and in the prior examinations with the predecessor T-Scan 2000 as reported in the previously approved PMA application.

Primary Endpoint: Relative Probability for Breast Cancer

The relative probability of a woman with a positive T-Scan ED examination having breast cancer was determined to be 4.95 (95% CI: 3.19-7.14). This was calculated by combining the per protocol results from the two arms of the study with the measured specificity of 94.7% and measured sensitivity of 26.4% and utilizing a conservative estimate of the prevalence of carcinoma in women age 30-39 as 1.5/1000 women (Kerlikowske *et al*. 1993). 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 thus meets the primary study success criterion.

Further, the prevalence of cancer in the study was approximately 41/1000 women, greater than the actual estimated prevalence of breast cancer in the intended use population of 1.5/1000. Proportionally increasing the total number of well women to reflect the prevalence of cancer in the study results in an adjusted odds ratio of 6.33.

Using the relative probability of 4.95, the resulting predicted probabilities indicate that approximately 1 in every 136 T-Scan ED positive women will have cancer. Thus, T-

Scan ED positive women are at significantly greater risk for breast cancer than their peers, who, on average, have a breast cancer risk of approximately 1 in every 666 women. Further, this level of risk is significantly greater than the average risk in women who are routinely offered mammography screening, which yields approximately 1 cancer per 400 mammograms performed (Bjurstam *et al*. 1997; Burhenne *et al*. 1992; Kerlilowske *et al*. 1993).

As discussed above, women who test positive on the T-Scan exam are at a breast cancer risk that is 4.95 times greater than their peers and, as shown in **Table 2**, have an absolute risk for breast cancer that is considerably greater than the risk associated with a positive family history of breast cancer. Perhaps most importantly, the absolute risk for breast cancer in T-Scan positive women is nearly three times greater (0.0073 vs. 0.0029[2]) than that of women age 40-49, who are routinely offered screening mammography. Thus, the T-Scan ED is highly effective as a means for pre-screening average risk, pre-menopausal women and identifying those who are at considerably elevated risk for breast cancer and should consider further imaging prior to the standard initiation of mammography at age 40.

Table 2

RELATIVE AND ABSOLUTE RISK FOR BREAST CANCER COMPARED TO STUDY SUCCESS THRESHOLD AND BASELINE PATIENT POPULATIONS

Patient Population	Relative Risk for Breast Cancer (95% CI)	Absolute Risk for Breast Cancer	
Pivotal Study Results (87 cancers, 1751 benign)	4.95 (3.16,7.14)	1:136	0.0073
Patient with first degree relative having breast cancer ("study threshold")	2.0	1:333	0.0030
Average risk women, 30-39	1.0	1:667	0.0015
Average risk women, 40-49	1.0	1:400	0.0029

2.6 U.S. ARMY MEDICAL RESEACH STUDY

The results of the T-Scan ED pivotal trial are consistent with the results of a prospective multi-center U.S. Army-funded study (Stojadinovic 2005). The U.S. Army is supporting a large, long-term study of the T-Scan ED to determine its role in identifying the risk for breast cancer in young women. This issue is of interest to the U.S. Army because more than 90% of women in uniform are under age 40, and more than 50% belong to ethnic minorities at increased risk for early-onset, biologically aggressive breast cancer. Interim results from this study included data on 1385 women. The sensitivity for cancer was 33% and the specificity was 93%. The data indicate that a T-Scan ED positive woman is

[2] Assuming that mammographic sensitivity is 85% (Livner 1996).

6 times more likely to have a high-risk lesion or cancer than a T-Scan ED negative woman.

2.7 CONCLUSIONS

The T-Scan ED is an important advancement in the breast cancer screening process. The device is intended for use in assessing breast cancer risk for women ages 30-39 by Ob/Gyn and other primary care physicians during routine physical exams. The pivotal clinical trial demonstrated that the relative probability of a woman with a positive T-Scan ED examination having cancer was 4.95 times greater than the average risk. Thus, a T-Scan ED positive woman is almost five times as likely as the average woman to have breast cancer.

Younger women with a positive T-Scan ED result are at a higher risk of having breast cancer than high-risk younger women who are routinely screened with mammography currently (risk of 1.7-2.0). Thus, screening T-Scan positive women with mammography is consistent with the current Standard of Care. This conclusion is further justified by a low false positive rate (5.3%).

There are approximately 20 million women between the ages of 30-39 in the U.S. If the prevalence of cancer is 1.5/1000 women, 30,000 cancers can be expected in this group of women, most of which will not be diagnosed until the woman starts screening mammography in her 40's. The T-Scan ED exam with follow-up mammography of T-Scan ED positive women therefore has the potential for identifying an additional 5,500 cancers (30,000 X 0.264 X 0.7).

Because all women tested with the T-Scan ED device are asymptomatic and without elevated risk, all T-Scan detected cancers would otherwise be neglected until the initiation of screening mammography at age 40.

3.0 FDA ISSUES AND MIRABEL RESPONSES

The following are issues identified for discussion by FDA, and a synopsis of the responses by Mirabel.

3.1 JUSTIFICATION FOR ENRICHED POPULATION FOR SENSITIVITY

Issue: Justification for use of an expanded age group in the Sensitivity Arm (women age 40-45), and rationale for applying the results to the target population (women age 30-39)

Response: The Sensitivity Arm was designed with an "enriched" population of women aged 40-45 in order to obtain a sufficient number of breast cancer cases to yield a reliable

measure of sensitivity. This was discussed with FDA, and agreed upon as a scientifically sound strategy, and the only feasible means of conducting a reasonably sized prospective breast cancer screening study in young women.

The inclusion of women age 40-45 is a valid means of enriching the Sensitivity Arm because it is widely accepted that breast tissue does not undergo any fundamental physiological change at age 40. The choice of 40 as the age at which mammographic screening is recommended is based on epidemiological studies of outcomes, not on a physiological rationale. Breast tissue is primarily affected by hormonal (or menopausal) status and not age.

All women who were peri- or post-menopausal were excluded from the Sensitivity Arm of the study, even if they were under the age of 40. It should also be noted that previous experience with EIS measurements has indicated that hormone changes occurring at menopause, and not at a specific age, affect breast electrical impedance characteristics **(**Piperno *et al*. 2002).

While there is no clinically valid reason to separate women age 30-39 from women age 40-45 in the pivotal study of the T-Scan ED, a comparison of baseline characteristics demonstrated that premenopausal women age 40-45 have sufficiently similar breast characteristics to women age 30-39 to justify pooling the data. A subgroup analysis of sensitivity including only women between the ages of 30-39 in the pivotal trial yields a value of 18.9%, which still exceeds the clinically relevant threshold of 2.0.

3.2 JUSTIFICATION FOR POOLING U.S. AND ISRAELI SITES

Issue: Validity of pooling data from centers in U.S. and Israel and ethnicity of subjects

Response: The pivotal trial of the T-Scan ED was conducted at 30 centers in the U.S. and Israel. A subgroup analysis of sensitivity results for U.S. vs. Israeli centers is not significant (Fisher's Exact Test; p=0.06). FDA conducted an independent analysis of these data using the Chi-square test (p=0.04). However, the Fisher's Exact Test is more appropriate than the Chi-Square as some expected values in the computation of the Chi-Square are less than 5.

Based on this statistical observation by FDA, Mirabel was requested to provide justification for pooling data from centers in the U.S. and Israel. This justification is based on application of well-established standards for the pooling of data in multi-center trials, as follows:

- All centers in the U.S. and Israel used the same study protocol, study devices and study procedures.

- No significant differences were found in patient characteristics, breast tissue, or medical practice.

- The automated nature of the algorithm calculation precludes any examiner bias in exam results.

- A blinded test evaluation of exam quality indicated no differences in exam quality between the two countries.

- Specificity for benign cases did not differ between the U.S. and Israel (81.75% vs. 80.12% respectively).

- Studies of T-Scan technology used to support approval of the previous PMA were conducted outside of the U.S. and no country-specific variation in breast tissue response was found.

- There is no known or reasonably postulated reason why the response of breast tissue to electrical impedance testing should be different in women from one country vs. another.

- The difference detected between centers in Israel and the U.S. is not statistically significant, and is most likely due to the fact that a higher number of cancer cases were seen in Israel. If one more cancer in the U.S. had been positive instead of negative, the significant Chi-square difference would disappear.

Finally, the U.S. Army is conducting a study at 5 sites in the U.S. involving 1385 patients, 64% of whom where White, 24% Black and 5% Hispanic. The interim results reported for this study found the T-Scan ED to have a sensitivity (33%) in the same range as measured in Israeli sites participating in the pivotal study (32.8%).

3.3 SENSITIVITY OF MAMMOGRAPHY

Issue: Sensitivity of mammography in young women

Response: The T-Scan device is designed to identify young women (age 30-39) who are at an increased risk for breast cancer and should consider mammography. Because the T-Scan device only identifies risk and does not offer an anatomical image of the breast, it is expected that most breast cancers in T-Scan positive women will be detected by the plain film or full field digital mammogram which is expected to follow a positive T-Scan result.

In estimating the expected benefit of incorporating the T-Scan device into the current screening regimen, the Company needed to evaluate what percentage of cancers in the target population would indeed be detected by mammography.

In all of the calculations presented to date, the Company utilized an estimate of 70% for average mammographic sensitivity in the target population of young women. However, in a recent meeting with FDA, the Agency stated that this estimate may be high and suggested that mammographic sensitivity might be closer to 50%. We evaluated the basis for this suggestion by FDA carefully but conclude, for the reasons provided below, that an estimate of 70% for average mammographic sensitivity in the target population is in fact the most appropriate and conservative benchmark.

Evaluation of FDA Estimate

During our discussion with FDA, the Agency mentioned that the source for their estimate is a recent *New England Journal of Medicine* article (Pisano *et al*. 2005) which compared digital to film mammography and included data on sensitivity in women under age 50.

This study estimated sensitivity in their film mammography arm for women under 50 to be in the range of 50%, and in their digital arm to be 78%. This figure of 50% sensitivity was also presented in FDA's calculations of the expected yield of T-Scan screening.

However, the Company is somewhat perplexed by the selection of this article because the authors specifically state in their discussion that their definition of sensitivity differs from the standard definition. On page 1779, the authors explain why the sensitivities of both digital and film mammography measured in this study are lower than the sensitivities in other studies. In this study, mammographic sensitivity was evaluated over the course of a year, while cancer incidence was evaluated over 455 days. Thus all cancers detected in the 90 days following the initial 365 days were counted as "false negatives". Not surprisingly this 25% difference in the detection window significantly lowered the reported sensitivity of mammography for all patients of all ages. Further, the article specifically references four seminal publications which represent the generally accepted sensitivity of mammography both in younger women and in women of all ages. These references appear in **Table 3** below and strongly support a sensitivity of 72-87% in the general population and a sensitivity of 72-83% in young women. It should be noted that due to the idiosyncrasies of the study reported in the NEJM, the calculated sensitivity of mammography for all ages was only 66%, again, approximately 15-20% below the sensitivity of mammography as commonly calculated.

Table 3

GENERALLY ACCEPTED SENSITIVITY OF MAMMOGRAPHY IN WOMEN

Reference	**Number of patients**	**Mammographic sensitivity**
Duffy *et al*. 1996 *Note : young women only*	**NA**	72-83%
Poplack *et al.* 2000	53,803	72.4%
Banks *et al*. 2004	122,355	86.6% (" neither sensitivity nor specificity varied significantly according to age")
Smith-Bindman *et al*. 2005	1,220,046	77%

In a more general review of published data, the figure of 50% sensitivity appears to differ significantly from most peer-reviewed publications that focus on the sensitivity of mammography in young women. In fact, the Company reviewed an extensive body of literature prior to suggesting 70% as the expected sensitivity, and selected this number because it reflects a conservative yet reasonable value of sensitivity as presented in the literature.

Table 4 below presents mammographic sensitivity found in young or pre-menopausal women. As can be seen from the table, the Company's use of 70% as mammographic sensitivity for the target population is closer to the bottom than the top of the range of reported sensitivities.

Table 4

MAMMOGRAPHIC SENSITIVITY FOUND IN YOUNG OR PRE-MENOPAUSAL WOMEN

Reference	Age Group	Mammographic sensitivity
Shaw de Parades 1990	$\leq$ 35	89%
Jefferies & Alder 1990	$\leq$ 35	86%
Kerlikowske *et al*. 2000	30-39	70%
Duffy *et al*. 1996	40-49	72-83%
Foxcroft *et al*. 2004	<40	71%
Wright *et al*. 2005	Pre-menopausal	67%

In summary, we believe that the mammographic sensitivity of 70% for breast cancer in younger women is appropriate and represents a conservative estimate. This figure is generally accepted and strongly supported by published data. Further, it should be recognized that the combination of ultrasound and mammography, as is commonly suggested for younger women, has been shown to be greater than 90% in certain studies (Kolb *et al.* 2002).

3.4 PREVALENCE OF BREAST CANCER IN YOUNGER WOMEN

Issue: Estimate of prevalence of breast cancer in women aged 30-39

Response: FDA noted that Mirabel Medical estimated that the prevalence of breast cancer in women age 30-39 is approximately 1.5 cancers per 1000 women. FDA described that in their review of incidence data from the SEER database, the reported incidence appears to be significantly lower, at approximately 0.5 cancers per 1000 women. FDA proposed that a lower incidence rate in the target population would result in a lower expectation for breast cancer detection rates in women offered T-Scan risk screening, thereby suggesting less clinical utility for the device.

The FDA asked the Company to justify the prevalence rate of 1.5 cancers per 1,000 women in the target population, and to specifically describe why data from Kerlikowske *et al*. (1993) as opposed to the SEER data, might be more relevant to the T-Scan breast cancer risk screening paradigm.

As requested by FDA, the Company response, below, addresses two specific issues:

1. **SEER data –Limitation of this database** in estimating prevalence of breast cancer in women 30-39, the target population.
2. **Estimating prevalence from studies in the target population –**Multiple studies in the literature support a conservative estimate of breast cancer rate of $\geq$ 1.5 cancers per 1,000 women in the target population.

1. SEER Data

SEER data relies on reports of cancer diagnosed, or incidence, but is not designed to measure prevalence - The SEER database offers a rich dataset composed of reported cancer cases from a wide population of women across the United States. However, because the SEER data only records the number of new cancer cases that are detected, diagnosed and reported, there is a fundamental under representation of cancers in young women whose breast cancers are generally not detected and diagnosed until the initiation of mammography at age 40. In fact, the SEER data reports a spike in incidence of approximately 100% between women age 34-39 and women age 40-44. This dramatic rise in incidence is much more likely to be associated with the initiation of mammography at age 40, and not an epidemic of breast cancers which spontaneously arise at age 40. For the purpose of evaluating the utility of the T-Scan device, the rate of existing (prevalent) but currently undetected cancers is much more relevant than the number of reported, detected and diagnosed cancers per the SEER database (incidence).

Additionally, it should be noted that SEER incidence numbers tend to be lower than those reported in most screening studies across all age groups. This disparity is associated with a host of factors, including the fact that only about 60% of women undergo routine cancer screening as recommended by clinical guidelines. Thus, the number of cancers diagnosed per age group across the entire country, as reported by SEER, is expected to be lower than the number of cancers detected in specific screening studies which explicitly screen an entire cohort of patients and help ensure their adherence to screening guidelines.

Because the SEER database does not address the question of existing but undetected breast cancers in the population of women age 30-39, additional academic sources were reviewed in order to establish a reasonable yet conservative estimate for the expected prevalence of breast cancer in women under the age of 40. These are described in the following section.

2. Estimating Prevalence from Studies in the Target Population

In discussions with FDA over the past three years or so, the Company has referred to a specific work (Kerlikowske *et al*. 1993) which expressly screened a large group of average risk women in the target population and reported a cancer rate of approximately 1.5 cancers per 1,000 women. This publication is one of many to report a similar prevalence in the target population. The Company (and many experts) relies upon the Kerlikowske data because it (a) reports a lower and therefore more conservative estimate than most other, similar studies and (b) specifically evaluated a large cohort of average risk women in the target age range and therefore offers a data set that is precisely representative of the T-Scan intended use population.

In addition to Kerlikowske *et al*. (1993), several other large published studies specifically report on the prevalence of breast cancer in populations of young women who are offered screening (see **Table 5** below).

FDA mentioned that potential limitations of the 1993 Kerlikowske publication might be the lack of geographic representation (the 1993 publications focused on a specific region of California) as well as the quality of screening mammography dating back nearly 15 years. In order to address these concerns, the table below includes two large trials that are both more recent and representative of a very diverse screening population (Bobo *et al*. 2000; Kerlikowske *et al*. 2000); the National Breast and Cervical Cancer Detection Program reported by Bobo *et al*. (2000) encompasses data from all 50 states, and reports a breast cancer rate of 1.5 cancers per thousand, while The National Cancer Institute Breast Cancer Surveillance Consortium data reported by Kerlikowske *et al*. (2000) includes data from California, Washington, New Mexico, Vermont, Colorado and New Hampshire and reports a breast cancer rate of 1.8 cancers per 1,000 women.

Table 5
PREVALENCE OF CANCERS IN A VARIETY OF UNITED STATES SCREENING STUDIES

Reference	Age range	Number of women	Number of cancers	(1) Prevalence (cancers/1000 women)	MX sensitivity	(2) MX detected prevalence (cancers/1000 women)
Destouet & Sherman, 1997*	<40	4402	5	**1.1**	0.82	0.9
Kerlikowske et al., 2000*		43906	78	**1.8**	0.68	1.2
Kerlikowske et al., 1996*		7308	22	**3.0**	0.77	2.3
Bobo et al., 2000*		11128	162	**1.5**	0.85	1.2
Liberman et al., 1993**		5105	8			**1.6**
Kolb et al.,2002*	40-49	5826	50	**8.5**	0.58	5.0
Burhenne et al., 1992**		4744	8			**1.7**
Kerlikowske et al.,1993**		9717	34			**3.0**
Kerlikowske et al., 1996		8833	45	**5.1**	0.87	4.4
Bjurstam et al., 1997*		9921	17	**1.9**	0.89	1.7
Destouet & Sherman, 1998*		14389	21	**1.5**	0.9	1.4
Bobo et al., 2000*		19117	679	**3.6**	0.89	3.2
Kerlikowske et al.,2000*		156359	459	**2.9**	0.76	2.2
Carney et al., 2003*		123114	343	**2.8**	0.67	1.9

**Studies in which the number of cancers identified is based on both mammography and the interval cancer rate (or cancers detected by other modalities i.e. ultrasound, MRI or CBE). In these cases the prevalence = number of cancers/total number of women; the mammographically detected prevalence = prevalence X mammographic sensitivity.*

*** Studies in which the prevalence rate is only estimated from the number of mammographically detected cancers.*

Specifically, the two large-scale studies by the NIH and NCI (Bobo *et al*. 2000; Kerlikowske *et al*. 2000) evaluating breast cancer rates in younger women had the following results:

- Bobo *et al*. (2000) evaluated 11,128 patients aged 30-39 and determined a breast cancer prevalence in the target population to be 1.5 cancers per thousand.
- Kerlikowski *et al*. (2000) evaluated 43,906 patients age 30-39 in the NIH Breast Cancer Surveillance Consortium and found 78 cancers in young women**.** A mammography adjusted breast cancer rate can be calculated from this study to be 1.8 cancers per 1000 women in the target population. Kerlikowske *et al*. (2000) analyzed separately women who did and did not have a family history of breast cancer. Of the 43,906 women in the study, 37,879 did not have a family history of breast cancer. Of these 59 were diagnosed as having breast cancer. The prevalence therefore in this population was 1.56/1000 women.

This data is consistent with the Kerlikowske *et al*. (1993) data also derived from a large mammographic screening study. Among the 30-39 year old women, three of the four estimates of prevalence are equal to or higher than the estimate derived from Kerlikowske *et al*. (1993). Hence, the Company feels that its estimate of 1.5 cancers/1000 women is, if anything, a conservative estimate of prevalence in the 30-39 year old age group.

Conclusion

In estimating breast cancer detection rates, significant differences can arise depending on whether incident cases are considered, or prevalence is used. For the purposes of this PMA, where the interest is in estimating the prevalence of breast cancer in non-high risk women under 39, who are not typically offered mammographic screening, the SEER population is inappropriate for estimating the expected rate of breast cancer.

However, the literature provides information on prevalence from studies that have specifically set out to determine the rate of breast cancer in young women by offering them mammography and thus estimating the number of cancers that are present in the population. In using this literature supported data, the Company has chosen a conservative estimate of 1.5 expected cancers per 1,000 women.

This figure, which is well supported, continues to demonstrate that T-Scan positive women in the 30-39 age group have a higher risk of having a breast cancer than those women age 40-49 who are currently recommended for annual mammography screening. Thus, it appears prudent to offer women who test positive on the T-Scan exam the same level of screening as would be offered to women who are between the ages of 40-49 and have a lower absolute risk for breast cancer.

3.5 RISKS OF IONIZING RADIATION

Issue: Exposure to ionizing radiation

Response: The T-Scan is designed help physicians recommend the consideration of a single digital or film mammogram to women who may be at increased risk for breast cancer based on a positive T-Scan result.

Exposure to ionizing radiation is generally considered when repeated exposure is expected over an extended period of time, or when evaluating women who are specifically susceptible to ionizing radiation, as postulated for women who are carriers of the BRCA 1 or BRCA 2. Exposure to ionizing radiation in women under 40 from a single mammogram is not considered a significant health risk in the context of a breast cancer risk that is significantly greater that the typical level of risk at which women are screened (Feig 2004; Jung 1998; Mettler et al., 1996).

The American Cancer Society reports that "While many people are worried about exposure to x-rays, the low level of radiation used for mammograms does not significantly increase the risk of breast cancer." However, certain studies do suggest that there is a link between mammograms performed and iatrogenic breast cancers. The BEIR V study, for example, indicated that up to 14 deaths could be attributed to mammography screening for every million mammograms performed in women who are in their 30's.

Projecting the pivotal study results on the population of approximately 20 million women between 30-39 in the U.S., and an expected breast cancer rate of 1.5 cancers per 1,000 women, it expected that offering the T-Scan exam to all U.S. women age 30-39 would generate approximately 1 million mammograms. If film mammography, having a sensitivity of 70%, is used to evaluate these women further, it is expected that approximately 5,500 cancers would be detected. If all T-Scan positive women were offered digital mammography, which has been shown to offer improved sensitivity in younger women, it is expected that the sensitivity would be approximately 78%, and that 6,100 cancer cases would be detected. In both cases, the cancer detection rate, ranging from 5,550 to 6,100 additional detected cancers appears to greatly outweigh the potential risk of 14 additional cancers. Even if the early detection of cancers in the intended population saves but a small fraction of deaths, the benefit - risk ratio in this case is high. More important perhaps, the benefit - risk ratio improves substantially when life years gained versus life years lost are considered because of the age at detection (and treatment) of the intended population as compared with anticipated death due to radiation-induced cancers.

Finally, according to the ACS "1 or 2 mammograms of every 1,000 leads to a diagnosis of cancer" (ACS 2006). Given the T-Scan ED pivotal study results, it is expected that T-Scan positive patients will have approximately 1 breast cancer per 136 women. Given a mammographic sensitivity of 70%, 1 cancer is expected to be detected per 250-300 mammograms. Thus, the risk to benefit ratio of mammograms performed per breast

cancer detected in T-Scan positive women is a significant improvement above the currently accepted Standard of Care and appears highly justifiable.

3.6 "BURDEN" ON HEALTHCARE SYSTEM

Issue: Burden to the health care system of false positives

Response:

The T-Scan ED device, and the EISYS™ algorithm development considered this issue prior to the development of the algorithm, and designed the thresholds such that patients who test positive on the device have a level of risk that is consistent with, or greater than, the risk at which women are currently screened with diagnostic modalities as per the Standard of Care.

Women who test positive on T-Scan ED are at a level of risk at which screening is routinely offered to other women.

Given that T-Scan ED-associated risk is greater than age-associated risk in women age 40-50, who are routinely offered mammography, we believe that the impact on the healthcare system is equitable and justified.

Additionally, Mirabel respectfully notes that the question of the cost or burden of healthcare delivery associated with a particular product is not a factor to be used by FDA in determining safety and effectiveness, based on the law and applicable regulations.

3.7 STABILITY OF ALGORITHM

Issue: Stability of the device algorithm

Response: FDA, and specifically, the Office of Science and Engineering Laboratories (OSEL) have carried out an extensive analysis of the manner in which the initial EISYS™ algorithm was developed, and the stability of the algorithm. These issues have been addressed, and extensive models have been run in which the algorithm was tested in a bootstrap simulation 1,000 times. Mirabel concludes, as did OSEL in their report, that the algorithm is stable. All answers regarding this topic were submitted to FDA in July 2005.

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4. Summary of Safety and Effectiveness

4.1 General Information

4.1.1 Device Generic Name

Trans-spectral Impedance (Breast) Scanner

4.1.2 Device Trade Name

T-Scan™ 2000ED (Early Detection)

4.1.3 Applicant's Name and Address

Mirabel Medical Systems Inc. (formerly TransScan Medical Inc.)
9020-1 Capitol of Texas Highway
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Austin, TX 78759

Israeli Office:
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Israel

4.1.4 PMA Number

P050003

4.1.5 Date of GMP Inspection

4.1.6 Date of Notice of Approval of Application

4.2 Indications For Use

The T-Scan 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.

4.3 Contraindications

The T-Scan ED is contraindicated in:

- Pregnant women; and
- Women implanted with electronic devices, *e.g.* pacemakers.

4.4 Warnings and Precautions

4.4.1 Warnings

The T-Scan ED is indicated for use as a complement to CBE in women ages 30 to 39 who do not have palpable lesions, family histories of breast cancer, or known genetic risks of breast cancer ("asymptomatic women of average risk"). This device does not replace conventional methods of detecting or diagnosing breast cancer, *i.e.*, CBE, mammography, magnetic resonance imaging ("MRI"), ultrasound ("US"), or biopsy evaluation, when appropriate.

The effectiveness of the T-Scan ED in identifying the risk of breast cancer in women who have palpable lesions identified by CBE, family histories of breast cancer, or known genetic risks of breast cancer has not been studied. The T-Scan ED is not a substitute for breast imaging, e.g., mammography or US, in symptomatic women and/or women of above average risk.

4.4.2 Precautions

- Patients with open or incompletely healed skin wounds over the areas to be examined should be treated with caution to avoid infection. If contamination with bodily fluids is suspected, thoroughly disinfect the scan surface probe using 96% ethyl or isopropyl alcohol.
- The T-Scan ED does not identify the specific location of suspicious tissue within the breast. Further breast examination, such as mammography or ultrasound, is necessary to localize the suspicious tissue.
- The T-Scan ED has not been tested on lactating women, women who have undergone chemotherapy, or women with recent biopsies. Physicians should interpret exam results from such women with care as their reliability has not been established.

- Care givers should evaluate the T-Scan ED results in conjunction with other clinical information, such as patient history, patient characteristics, and the results of other tests, in determining the appropriate management for that patient.

- Use of the T-Scan™ is limited to medical professionals who have been trained in the use of the device for identifying women at higher risk of breast cancer.

- The T-Scan ED must be used only in accordance with the User Manual, which is provided.

- In order to prevent potential injury, do not remove covers or panels of the T-Scan ED.

- Do not attempt to modify or repair the T-Scan ED. Installation and servicing should be performed by qualified service personnel only.

- The T-Scan ED patient contact surfaces should be thoroughly cleaned between patients. A soft material (cloth, paper towel, or alcohol wipe) and alcohol should be used to thoroughly clean the entire surface of the scan probe of residual gel or conductive material after each examination. Failure to do so can result in the surface probe producing inaccurate recordings.

4.5 Device Description

T-Scan ED is a real-time, noninvasive, radiation-free device that measures and analyzes the electrical impedance properties of breast tissue.

4.5.1 Device Components

T-Scan ED is available in a desktop configuration and a cart configuration. The cart supports the main PC (hidden behind a door), the PC accessories (keyboard and trackball) and the screen, which is mounted on a movable mount for operator convenience. The main components of the desktop and cart configurations are:

- An isolation transformer (behind the door), isolating the applied parts (surface probe and source electrode) from the external ground and lines;

- The main console housing a PC (behind the door) and **[Redacted]**. The **[Redacted]** a PCI card and uses the PCI bus for commands and for data transfer;

- A surface probe, which is a hand-held, multi-electrode unit, which the operator places in contact with the patient's breast when performing a scan;

- A signal transmitter, which is a stainless steel cylinder held by the patient hand;

- PC input/output peripherals, which include a monitor, keyboard, and trackball, all of which are mounted on top of the cart (for user convenience) and an optional CD read-write drive; and

- A laser printer.

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

4.5.2 Device Operation

Detection of malignant tissue is based on the large inherent differences in capacitance and resistance between neoplastic tissue and surrounding normal tissue. In-vitro measurements on freshly excised breast tissue have shown that malignant tissue has lower electrical impedance than normal tissue or benign lesions (Jossinet, 1996, 1998; Morimoto, 1990; Surowiec *et al*., 1988).

The T-Scan ED measures tissue electrical impedance over **[Redacted]** of frequencies **[Redacted]**, by applying an electrical signal (approximately **[Redacted]**) via a Signal Transmitter held by the patient in her hand contralateral to the breast being examined, and detecting the resulting electric currents at each of 64 sensors in a 8 x 8 array on a surface probe placed on the breast being examined. Hardware and software controls limit the voltage and the resulting current to safe levels **[Redacted]** , as demonstrated by the more than 10,000 examinations performed with T-Scan™ since 1994 without any adverse events. The safety circuits are identical to the T-Scan™ 2000, which the Food and Drug Administration ("FDA" or "the Agency") approved on April 16, 1999 (P970033). The safety circuit works as follows:

> The transmitted current passes through a series resistor of **[Redacted]**. A differential amplifier measures the voltage on the resistor and carries it to a comparator, where it is compared to reference voltage. If the measured voltage exceeds the reference – the comparator opens a switch, thus disconnecting the signal transmitter from the source, and blocking the signal from contact with the patient. This also causes the software to output a warning message on the device monitor.

The following tests are performed <u>before every patient exam</u> to ensure the safe operation of the over-current circuit:

1. Operation of the circuit is tested by closing an auxiliary switch, which causes electric current to flow through resistor R2. A reference voltage, equal to the expected voltage on R1, is sent to the comparator. The comparator compares the actual voltage on R1 to the reference voltage, and disallows the measurement if the values do not match;

2. The over-current flag is tested by sending a low reference word to the comparator and testing the flipping of the flag; and

3. The reference word is tested, to assure its value.

The electrical capacitance and conductance (the inverse of the resistance) at each sensor are computed for each frequency. Thus, capacitance and conductance (rather than the resistance) are the natural tissue parameters. The device displays an image of both breasts, which the operator uses solely to position the surface probe and obtain an artifact-free image. (As explained in more detail below, areas where there is poor contact between the surface probe and the skin or air bubbles in the gel appear as black regions in the image.) The map is not used for any clinical determination. A vertical dynamic bar also indicates the quality of the reading. The device analyzes the multi-frequency data and produces a binary outcome of negative (normal tissue) or positive (some tissue suspected of being malignant, *i.e.,* suspicious). It utilizes data from 18 sectors (9 sectors for each breast) taken at the 17 default frequencies which range from **[Redacted]**. For each sector and for each frequency, the measured conductivity and capacitance values are averaged over all the sector pixels. The set of resulting averages is multiplied by a set of coefficients (evaluated on learning group, as explained below) and compiled to generate the algorithm result. The device displays a solid green horizontal line if the result is negative or a red hatched line if the result is positive below a diagram of both breasts. Thus, the device clearly and automatically indicates whether the results are negative or positive; the physician does not interpret the image or the underling data to make determination of normal or benign.

The T-Scan ED is a modification of the Company's T-Scan™ 2000, which the FDA approved on April 16, 1999 (P970033). As described below in Table 4-1, the T-Scan ED has very similar technological characteristics and principles of operation as the approved T-Scan™ 2000, even though they have different indications.

4.6 Alternate Practices and Procedures

The T-Scan ED's intended patient population is women between the age of 30 and 39 who do not have palpable lesions and/or high risk factors. Since these women are younger than the current minimum recommended age for screening mammography, the only breast cancer detection examination they usually receive is CBE. The T-Scan ED is a complement to, and not a substitute for, CBE in that it is indicated for use only in women who do not have palpable lesions detected by CBE. The T-Scan ED examination is performed after CBE in women who would otherwise not receive further breast evaluations. A positive T-Scan ED result provides additional information for the physician to consider in deciding whether to refer the women for additional breast evaluations.

The T-Scan ED supplements current modalities used in the detection and diagnosis of breast lesions, *i.e.,* CBE, mammography, sonography, MRI, nuclear medicine, computed tomography, surgical biopsy, core biopsy and fine needle aspiration. It is not an alternative to any current breast cancer detection, diagnosis procedure or device.

The T-Scan ED is a radiation free, low risk device. Thus, T-Scan ED provides a substantial benefit to an underserved population of young women who are at risk for significant mortality and morbidity if their breast cancer is not detected in a timely manor.

4.7 Marketing History

Mirabel Medical Systems Inc. (formerly "TransScan") began developing breast impedance devices for commercial clinical applications in 1993.

The Israel Ministry of Health approved the T-Scan™ 2000 as an adjunct to conventional breast examination methods. Similar approval was obtained in Russia in April 1997. The T-Scan™ 2000 received premarket approval from the FDA on April 16, 1999 (P970033). Both the clinical community and the company discovered that usefulness of an additional imaging adjunct to mammography was somewhat limited from a marketing perspective. Thus, the Company elected not to market the T-Scan™ 2000 in the United States ("U.S."), but instead to focus on further developing the platform technology.

As noted above, the T-Scan ED is a modification to the approved T-Scan™ 2000. The Israeli Ministry of Health granted a Certificate of Free Sale to the T-Scan ED device in April, 2003. A CE Mark was first issued in December, 2002 and reissued in November, 2003 (CE # 75211CE01. KEMA EC Notified Body Identification Number 0344). However, the Company has chosen not to market the device outside of the U.S. until

FDA approves this PMA supplement, which contains U.S. and international clinical data demonstrating that the device is safe and effective for its new indication.

4.8 Potential Adverse Effects Of The Device On Health

The T-Scan ED is a very low risk device. It analyzes the electrical impedance parameters of breast tissue by means of an external transducer placed on the breast that measures electrical signals generated by a hand-held source electrode over multiple frequencies ranging from **[Redacted]**. The entire procedure lasts approximately six minutes. The device is radiation-free diagnosing the human tissue by transmitting low-level voltage and measuring the current. The safety circuits of the T-Scan ED are identical to its predecessor, the T-Scan™ 2000, and are described in section 4.5.2, above. Also, the applied parts (the signal transmitter and the surface probe) of both systems are isolated from the power mains by means of an isolation transformer, so the patient is protected from spikes or shocks on the mains ground line. The device complies with IEC 60601-1 and IEC 60601-1-2. Importantly, no adverse effects have been reported during the clinical studies of the T-Scan ED or the T-Scan™ 2000, which collectively have been tested on more than 10,000 women.

4.9 Summary of Pre-Clinical Studies

4.9.1 Bench Studies

The T-Scan ED complies with 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. The test reports are given in **Appendices 8.1 and 8.2**.

4.9.2 Operational Safety Analysis And Precautions

A risk analysis is provided in **Appendix 6.5.1**.

4.9.3 Software Safety Tests

T-Scan ED software provides safety tests that assure proper functioning. Every released version is tested and the results are documented. Tests include:

1. Proper connection of the surface probe and the signal transmitter.

2. Proper functioning of the system's voltage-limiting circuit.

3. Proper calculation of algorithm results. This is done by recalculation of data from an existing (anonymous) database. Partial results of the computation are also checked, including the electrical parameters, the signal-to-noise ratio ("SNR"), and the numerical results of the algorithm.

4.9.4 Biocompatibility

The only components of the T-Scan ED that contact the patient or the operators are the hand-held surface probe and the signal transmitter. The PMA-approved T-Scan 2000 contains the same hand-held surface probe and signal transmitter, which are composed of the same materials and are obtained from the same supplier. Thus, FDA's approval of the T-Scan™ 2000 demonstrates the biocompatibility of the T-Scan ED. Therefore, biocompatibility testing of the T-Scan ED is not necessary to show that this device is biocompatible.

In addition, more than 10,000 women have undergone T-Scan™ examinations during the past ten years, without any reported incidents of irritation, inflammation or any other discomfort. Thus, the actual use of this device supports its biocompatibility.

4.9.5 Animal Studies

Mirabel has not conducted any animal testing of the T-Scan ED for several reasons. First, the amount of electrical energy that the device delivers to the patient is within the range that is considered safe. Second, 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, Mirabel has already established the safety of the device and its effectiveness for that general intended use. Third, the T-Scan ED utilizes electrical parameters of 18 sectors and a weighted-sum algorithm. The coefficients of the algorithm are strongly related to the physiology of the measured sectors. For example, frequency-dependent coefficients are used for the **[Redacted]** sector that cannot be used for other sectors. Therefore, the method is specific to analyzing breasts of human females; an animal model would not provide useful information. Thus, Mirabel determined that the established safety and effectiveness profile of the T-Scan™ 2000 justified conducting clinical testing of the device.

4.10 Summary of Clinical Studies

4.10.1 Overview of Clinical Studies

The T-Scan exam is intended to be used for identifying women between ages 30 –39 who are at increased risk for breast cancer, but who would be overlooked by the current reliance upon family history as the primary means for the identification of risk. Two clinical studies have been conducted to evaluate the clinical safety and effectiveness of the T-Scan ED. An initial pilot study was conducted in 2002-2003 in order to evaluate

the feasibility of combining a post-processing algorithm with the core EIS technology. A second, pivotal trial was developed with input from FDA in order to provide reliable estimates of sensitivity and specificity and, in turn, estimate the device's ability to detect tissue changes and identify breast cancer risk in the target population. Based upon the current standard of care, whereby women with a relative risk of 2.0 or more are considered "at risk" and offered additional imaging, greater surveillance and enrollment in specific management protocols (Kramer and Brown, 2004; Pharoah *et al*., 2000; Tilanus-Lindthorst *et al.,* 2000), the FDA, clinical investigators and the Company agreed that a positive T-Scan ED result would need to reflect a risk of 2.0 or more to be clinically useful. Thus the primary endpoint of the pivotal study was to determine if a woman who is positive on a T-Scan ED exam is at a risk for breast cancer that is, at least, 2 or more times greater than the expected risk in the general target population.

4.10.2 Pilot Study

Pilot study data were collected using an experimental algorithm. The purpose of this pilot study was:

- To determine if the core EIS technology, coupled with an experimental processing algorithm could achieve a high (>90%) level of specificity.
- To collect data for further development of an algorithm offering high specificity and clinically useful sensitivity, incorporating higher frequency recordings. (To this end the T-Scan ED recorded **[Redacted]**.

Study Design

The pilot study was conducted at 14 medical centers on a total of 1,708 women ranging in age from 17-77 years. Patients presenting at the medical center for screening mammography, ultrasound, annual gynecological exam or breast biopsy were offered enrollment in the study.

Women without cancer were classified in one of two clinical categories:

- Screening cases – These "clinically benign" cases consist of asymptomatic women who had a routine, normal CBE and women who had scheduled routine screening with mammography or US and found to show no evidence of breast cancer. This category also includes women who had a breast finding that was considered benign by the examining physician and thus did not warrant biopsy or further evaluation.
- Benign cases – These "histologically benign" subjects consist of cases where the patient underwent biopsy based on CBE and/or an imaging study, and was found to be histologically benign.

Apart from allowing a technologist to perform a T-Scan™ exam prior to their scheduled appointment or procedure, patients who enrolled in the T-Scan study followed their regular clinical course regardless of T-Scan result.

Sensitivity of the device was estimated by comparing the rate of T-Scan™ positive results with the number of biopsy proven cancers. Specificity was evaluated based on the assumption that women did not have breast cancer if:

- they were normal on all other performed screening examinations (CBE, US and/or mammography), or
- they had lesions that were not deemed sufficiently suspicious to warrant biopsy, or
- they had biopsy-proven benign lesions.

Sensitivity and specificity for various clinical categories are shown in Table 4.2 below.

Table 4.2. Specificity and sensitivity at all study sites (Pilot Study)

	N	**Specificity**
Screening Cases	1352	92.6%
Benign/Biopsy Cases	295	93.9%
Total non-cancer	1647	92.8%
	N	**Sensitivity**
Cancer Cases	61	11.5%

Using logistic regression, there was no significant relationship between specificity and presence or absence of a palpable lesion or patient age. The logistic regression examining the relationship between sensitivity and palpability and age also did not reach statistical significance.

Sensitivity tended to be higher for small (≤10 mm) lesions (18.8% (3/16)) than for larger (>10mm) lesions (8.3% (3/36)). The smallest cancer detected by EIS in this study was 7 mm in size.

Conclusion

Data from the pilot study indicated that it was indeed possible to construct an EIS algorithm that could consistently operate at a level of very high specificity. Specifically, it was determined 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 **[Redacted]**.

Using data from the pilot study, a sub-analysis looking at the high-frequency data was performed on a cohort of patients under the age of 46. Results of this analysis indicated that the combination of higher frequencies with a high-specificity post-processing

algorithm may be of specific value in identifying electrical impedance characteristics associated with small (< 20 mm lesions) in a background of dense breast tissue.

The assimilation of clinical and physical factors, as described above, formed the basis of the EISYS algorithm.

4.10.3 Pivotal Study

Overview

A multicenter prospective study was conducted to specifically evaluate 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 ED. All per-protocol cases included in the Specificity Arm of this study were in the intended use population of women age 30-39. In the Sensitivity Arm, however, an expanded age range (30-45) of pre-menopausal women was accepted by FDA in order to allow more expeditious accrual of patients while maintaining breast tissue characteristics that are consistent with the target age range.

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 (S_n), specificity (S_p), and the prevalence of cancer in the population (R_{ca}).

4.10.3.1. Specificity Arm

Introduction

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

Study Design

Study subjects in the Specificity Arm of the study consisted of 1946 women enrolled at 17 clinical sites in Israel and the U.S., who had no breast related signs or symptoms and who visited their Ob/Gyn or breast center for an annual physical exam.

Patients meeting the following eligibility criteria were considered enrolled in the study upon signing the informed consent.

Prior to enrollment in the Specificity Arm of the study, candidates had to meet the following criteria:

- Women age 30-39 inclusive; and

- Not pregnant.

Candidates were excluded from this study if prior to enrollment they met any of the following exclusion criteria:

- Pregnant;
- 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.

All patients had a CBE by a qualified examiner (typically the referring physician or the principal investigator). Specific attention was paid to the CBE and the presence or absence of a palpable breast mass. Women were also questioned regarding potential covariates such as hormone use, brassiere size and family history of breast cancer. Since no women presented signs or symptoms of breast cancer, it was assumed that all women in the Specificity Arm of the study were free of breast cancer.

Patient Population

Of the 1946 women enrolled, 1935 T-Scan examinations were completed, of which 1751 were completed per protocol. Exams or subjects were excluded from the per protocol analysis based on: patients not meeting the eligibility criteria (179); technical difficulties during the T-Scan examination (18); and patients declining exam after enrollment (2). Table 4.3 below shows the distribution of baseline characteristics that may be associated with the T-Scan exam results.

Table 4.3. Baseline Characteristics (Specificity Arm)

Baseline Characteristics	N	%
Menopausal Status		
Pre-Menopausal	1718	98.1%
Post-Menopausal	32	1.8%

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Missing	1	0.1%
Hormone Usage		
No hormone use	968	55.3%
Estrogen compounds	588	33.6%
Progesterone only compounds	96	5.5%
Other	15	0.9%
Missing	84	4.8%
Brassiere Cup Size		
A or B	839	47.9%
C or D	794	45.3%
More than D	84	4.8%
Missing	34	1.9%
Number of 1st degree relatives with breast cancer		
0	1558	89.0%
1 or more	163	9.3%
Missing	30	1.7%
Race/Ethnicity		
Asian	26	1.5%
American Indian	9	0.5%
Black	51	2.9%
Hispanic	48	2.7%
Caucasian	865	49.4%
Missing	752	42.9%
Age		
Mean (Std.)	1751	34.7 (2.8)
Range	1751	30 – 39

Results

Table 4.4 below shows the overall specificity results for all completed T-Scan exams and the per protocol T-Scan exams.

Table 4.4. Overall specificity (Specificity Arm)

Patient Population	N	T-Scan™ Negative	Specificity
Per protocol	1751	1658	94.7%
All data available*	1933	1827	94.5%

**All data available includes all patients with a valid T-Scan™ result*

Of the cases excluded from the per protocol analysis, perhaps the most important subgroup is that of women with an abnormal CBE (palpable mass). Specificity for women with normal and those with abnormal CBE is shown in table 4.5 below.

Table 4.5. Specificity by CBE result (Specificity Arm)

	N	T-Scan™ negative	Specificity	p-value
Normal CBE	1751	1658	94.7%	0.94
Abnormal CBE	59	56	94.9%	

While this subgroup is not clinically relevant to the target population, since women with a palpable mass are not indicated for a T-Scan, it is nevertheless relevant to the interpretation of data in the Sensitivity Arm of this study (see below) where a large proportion of women had palpable lesions.

Data presented in the tables above strongly suggest that the inclusion of all cases (including those excluded for technical problems) has a negligible impact on the overall estimates of device specificity (94.5% vs. 94.7%). The remainder of the analysis is devoted to the per protocol cases so as to adequately reflect results in the intended use population.

Pearson's chi-square was also used to examine the relationship between specificity and brassiere cup size, menopausal status, hormone use and family history. Specificity in each of these groups is shown in Table 11.10. There was no significant ($p>0.05$) correlation between EIS results and family history, menopausal status, and use of exogenous hormones.

Brassiere cup size was associated (Pearson $\chi 2=16.6$ $p=0.001$) with positive EIS findings; namely, the rate of FP exams increased with increasing cup size. However, it should be noted that even in the largest cup sizes (which represented <5% of patients), specificity was almost 91%.

The overall specificity for per protocol cases in the Specificity Arm was 94.7%. This specificity was unaffected by presence of a palpable mass, menopausal status, hormone use, or family history of breast cancer. It was significantly related to brassiere cup size, being lower (although still above 90%) for larger breasted women.

Safety

There were no reported cardiac, neurological, dermal, thermal or allergic reactions or adverse events, nor any reports of patient discomfort. 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 application.

4.10.3.2. Sensitivity (Biopsy) Arm

The main objective in this arm of the study was to evaluate the T-Scan device's sensitivity for cancer. In addition, specificity for benign lesions was a secondary objective and was also estimated in this arm of the study. The Specificity Arm was designed to estimate specificity in the intended use population (*i.e.*, women age 30-39 without a palpable mass). However, in designing the Sensitivity Arm, it was impracticable to limit the study subjects to the intended use population. In discussion with FDA it was agreed that the Company could use an enriched population including women age 30-45 and women with palpable lesions.

Study Design

Study subjects in the Sensitivity Arm consisted of 597 women enrolled at 18 clinical sites in Israel and the U.S. Subjects were to be between the ages of 30 and 45 (inclusive) who had a suspicious breast lesion based on results of a CBE, mammography, US or MRI and had been referred for breast biopsy. This arm of the study involved testing women prior to their biopsy procedure. The expansion of the age range to 45 for the collection of data on cancers allowed the Company to collect data on sensitivity on a more reasonable number of patients than would have been possible if the age of the study population were restricted to patients under the age of 40.

Women were considered positive for breast cancer only if they had histological confirmation of malignancy. Histological diagnosis was performed by experienced breast pathologists. For the purposes of this study, atypical hyperplasia and lobular carcinoma in situ (LCIS) were regarded as a benign finding, and not a malignant lesion.

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 of the study, except that women with a palpable mass were excluded from the Specificity Arm and included in the Sensitivity Arm.

Patient Population

Of the 597 women enrolled, 545 completed T-Scan exams and biopsy results, of which 390 had exams completed per protocol (303 benign cases; 87 cancer cases). Exams were excluded from the per protocol analysis based on patients not meeting the eligibility criteria (89), no biopsy results (44), technical difficulties during the T-Scan examination (70), and patients declining exam after enrollment (4).

Table 4.6 below shows the distribution of baseline characteristics for patients with T-Scan exams completed per protocol that may be associated with the T-Scan exam results.

Table 4.6. Baseline Characteristics (Sensitivity Arm)

Baseline Characteristic	Cancer Cases (N=87)		Benign Cases (N=303)		Total Cases (N=390)	
	N	%	N	%	N	%
Age						
30-39	37	42.53%	142	46.86%	179	45.90%
40-45	50	57.47%	161	53.14%	211	54.10%
Mean (Std)	87	39.5 (3.9)	303	38.8 (4.3)	390	38.9 (4.2)
Range	87	30 - 45	303	30 - 45	390	30 - 45
CBE						
Normal CBE	17	19.54%	131	43.23%	148	37.9%
Abnormal CBE	70	80.46%	172	56.77%	242	62.1%
Hormone Usage						
No hormone use	57	65.5%	227	74.9%	284	72.8%
Compounds with estrogen (with or without progesterone)	7	8.0%	21	6.9%	28	7.2%
Compounds with only progesterone	2	2.3%	6	2.0%	8	2.1%
Other	1	1.1%	6	2.0%	7	1.8%
Missing	20	23.0%	43	14.2%	63	16.2%
Bra Cup Size						
A and B	26	29.9%	121	39.9%	147	37.7%
C and D	34	39.0%	133	43.9%	167	42.8%
>D	3	3.4%	23	7.6%	26	6.7%
Missing	24	27.6%	26	8.6%	50	12.8%

Baseline Characteristic	Cancer Cases (N=87)		Benign Cases (N=303)		Total Cases (N=390)	
	N	%	N	%	N	%

Number of First Degree Relatives with Breast Cancer						
None	68	78.2%	248	81.8%	316	81.0%
One or more	13	14.9%	52	17.2%	65	16.7%
Missing	6	6.9%	3	1.0%	9	2.3%
Size of Lesion (mm)						
≤ 20	45	51.7%	165	54.5%	210	53.8%
> 20	27	31.0%	39	12.9%	66	16.9%
Missing	15	17.2%	99	32.7%	114	29.2%
Mean (Std)	72	22.9 (15.1)	204	15.8 (9.8)	276	17.6 (11.8)
Range	72	5-80	204	3-78	276	3-80

Results

Table 4.7 below shows the overall sensitivity results for all completed T-Scan exams (n=70) and the completed, per protocol, T-Scan exams (n=90) in women with pathology confirmed cancers.

Table 4.7. Overall sensitivity (Sensitivity Arm)

Patient Population	N	T-Scan™ Positive	Sensitivity
Per protocol	87	23	26.4%
All data available	131	30	22.9%

Pearson's chi-square was used to examine the relationship between sensitivity and each of the above covariates. There was no significant ($p > 0.10$) correlation between EIS results and the above categorizations of patient age, brassiere cup size, hormone use, family history or cancer, palpability of lesion and cancer (lesion) size.

Although women with symptomatic breast pathology are not part of the intended use population, specificity was examined in the Sensitivity Arm of the study in order to validate the non-random aspect of the technology. The overall specificity results for all completed T-Scan exams (n=414) and the completed, per protocol, T-Scan exams (n=309) are shown in the following Table 4.8.

Table 4.8. Overall specificity (Sensitivity Arm)

Patient Population	N	T-Scan™ Negative	Specificity
Per protocol	303	245	80.9%
All data available	414	339	81.9%

As in the Specificity Arm of the study, brassiere cup size was associated with positive EIS findings ($p < 0.001$).

As shown above, the overall sensitivity for cancers was 26.4% and specificity for benign lesions was 80.9%. Neither sensitivity nor specificity for benign lesions was related to the covariates of palpability, family history, or hormone use. Specificity for benign lesions was related to bra size and was higher for those women with smaller bra cup sizes. Sensitivity showed a statistically non-significant relationship with cancer size being higher for smaller cancers. Although this difference was not statistically significant, it was consistent with the trend found in other EIS studies of a higher sensitivity for small cancers.

Safety

There were no reported cardiac, neurological, dermal, thermal, allergic reactions or adverse events, nor any reports of patient discomfort. This result confirmed similar findings in the pilot study and in the prior examinations with the predecessor T-Scan™ 2000 as reported in the previously approved PMA application

4.10.3.3 Combined Results of the Two Arms of the Study

The anticipated clinical efficacy of the T-Scan device for breast cancer risk assessment in 30-39 year old asymptomatic women of average familial risk is directly related to the T-Scan's competence in identifying electrical impedance measurements that are associated with an increased potential for malignancy.

In order to measure device performance, this study specifically assessed the rates of sensitivity and specificity in a population of patients that closely resemble the intended use population. The measured results of sensitivity and specificity along with data on the prevalence of cancer in the intended use population were used to estimate "relative probability", that is 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 used to calculate relative probability for breast cancer.

$$P_r = \frac{S_n}{S_n R_{ca} + (1\text{-}Sp)\,(1 - R_{ca})}$$

In this formula, the relative probability (P_r) is a function of the sensitivity (S_n), specificity (S_p), and the prevalence of cancer in the population (R_{ca}).

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On this basis, 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. Thus, to be considered efficacious, a positive T-Scan result would need to correlate with a breast cancer risk of ≥ 2.0 in the target population. For example, if published data indicates that the prevalence of breast cancer in the target population is 1.5 /1,000, then the average "per patient" risk is 1 cancer per 667 women (1,000/1.5). If a device identifies women who have a relative risk of 2, it would identify a cohort that had a risk of 1 cancer in 333 women.

Results

Combining the per protocol results from the two arms of the study with the measured specificity of **94.7%** (1658/1751) and measured sensitivity of **26.4%** (23/87) and utilizing the prevalence of carcinoma in women age 30-39 as 1.5/1000 women (Kerlikowske *et al*., 1993), the relative probability of a woman with a positive T-Scan examination having cancer was **4.95** with a 95% confidence interval estimated by bootstrapping methods of (3.16, 7.14). 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 thus meets the primary study success criterion.

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. 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 from women under the age of 40, the relative probability based on the specificity arm results of 94.7% and the sensitivity arm results (18.9%) in women ages 30 to 39 was 3.6 with a 95% confidence interval of (1.4, 6.2) which still exceeds the 2.0 threshold.

Additional estimates of efficacy

The data from this study can also be used to calculate the positive predictive value and odds ratio associated with the T-Scan examination. Complete data from both arms of the clinical study is summarized in Table 4.9 below.

Table 4.9. T-Scan results by lesion classification

T-Scan™	Normal	Benign	Malignant	Total
Negative	1,658 (94.7%)	245 (80.9%)	64 (73.6%)	1967 (91.9%)
Positive	93 (5.3%)	58 (19.1%)	23 (26.4%)	174 (8.1%)
Total	1,751 (100%)	303 (100%)	87(100%)	2,141 (100%)

As can be seen in the study summary table, above, the prevalence of cancer in the study was 70/2,035 or ~ 34/1,000 women. This number is significantly greater than the actual estimated prevalence of breast cancer in the intended use population of 1.5 cancers per 1000 women. In order to more accurately represent the intended use population, the following Table 4.9.1 proportionally increases the total number of well women aged 30-39 in the Normal column to maintain the accepted ratio between well women and expected cancer cases. Thus, the well woman population is inflated from the actual 1,751 to a projected 46,383.

Table 4.9.1. Projected T-Scan results in the intended use population

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%)	58000 (100%)

The above table can be further collapsed to show cancer vs. non-cancerous patients.

T-scan results in cancer and non-cancer cases

T-Scan™	Non-Cancer Cases	Cancer Cases	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%)	58000 (100%)

The projected data in the above 2x2 contingency table was analyzed by using logistic regression to find a strong dependence of the ordered categories of non-cancer cases and cancer cases on negative or positive T-Scan™ test results, with adjusted odds ratio = 6.33 and corresponding 95% confidence interval (CI) = 3.93-10.21. These results strongly indicate that women with positive T-Scan™ exam results have substantially greater odds of having malignant lesions than women with negative T-Scan™ test results.

Additionally, resulting in the corresponding predicted probabilities:
Pr(Cancer| Negative Test Result) = 0.00117 with 95% CI = (0.00091 - 0.00149);
Pr(Non-Cancer| Negative Test Result) = 0.99883.
Pr(Cancer| Positive Test Result) = 0.00734 with 95% CI = (0.00488 - 0.01102); Pr(Non-Cancer| Positive Test Result) = 0.9266.
These results indicate that approximately 1 in every 136 positive T-Scan™ results will be a cancer case.

4.11 Conclusions Drawn from Studies

4.11.1 Risk/Benefit Analysis

The T-Scan device for breast cancer risk assessment in 30-39 year old, asymptomatic women is able to identify women that are at increased risk for potential for malignancy. The data from this study indicate that women who are positive on T-Scan have a probability of having breast cancer that is more than six times greater than that for a woman randomly selected from the population at large. Additionally, in the population of 30-39 year old women, there is on average about one cancer case for every 667 women. In contrast, among T-Scan positive women, there will be one cancer case for every 110 women. Thus, T-Scan positivity, like a significant family history, identifies specific women who fall well within the accepted yield for mammographic screening. In fact, the relative probability for breast cancer in women with T-Scan positivity not only exceeded the primary success criterion, but also compares favorably with the relative risk associated with other factors (*e.g.,* genetic factors (Schwab *et al*., 2002) and previous breast cancer (Feig *et al*., 1998) that are generally considered stronger justifications for screening mammography or even the initiation of preventative measures.

4.11.2 Safety

The T-Scan ED's conformance to IEC 60601-1 and 60601-1-2 demonstrates the electrical safety and electromagnetic compatibility of this device. No serious device-related adverse events occurred in the clinical studies.

4.11.3 Effectiveness

Clinical data show that women with positive T-Scan ED results have a significantly higher risk of having breast cancer compared to women in the general population. Thus, the T-Scan ED is safe and effective for use as a complement to CBE in women aged 30 to 39, inclusive, who do not have any palpable lesions detected by CBE or a family history of, or genetic risk factors for, breast cancer to detect differences in tissue associated with an increased risk of breast concern. A positive T-Scan™ result provides physicians with additional information to guide a recommendation regarding further breast examination, *e.g.,* mammography, MRI, or US.

4.12 FDA Decision

4.13 Approval Specifications

4.14 References

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5. Device Description

Overview

T-Scan™ 2000ED (Early Detection) is a noninvasive and radiation-free device for breast cancer risk detection in asymptomatic women who are younger than the recommended minimum age for screening mammography. The device is based on electrical impedance scanning ("EIS") that maps the local impedance properties of breast tissue (Assenheimer et al, 2001; Scholtz and Anderson, 2000). Detection of cancer by EIS is based on the large inherent differences in capacitance and resistance between neoplastic tissue and surrounding normal tissue. Large differences in electrical impedance between malignant tumors and normal breast tissue or benign lesions have been reported by in-vitro measurements on freshly excised breast tissue (Fricke and Morse, 1926; Jossinet, 1996, 1998; Morimoto et al., 1990; Suroweic et al., 1988).

T-Scan ED non-invasively maps the local distribution of tissue electrical impedance at various frequencies. Specifically, the T-Scan ED measures tissue electrical impedance over four **[Redacted]** ,by applying an electrical signal (approximately 1 volt) via a signal transmitter, which is a reference electrode, that is held in the hand of the patient contralateral to the breast being examined. A Surface Probe placed on the breast being examined detects the resulting electric currents. A conductive (ultrasound) gel, which is not supplied with the device, is applied to the signal transmitter and the scan probe.

For each frequency, the electrical capacitance and conductance at each of **[Redacted]** sensors on the underside of the surface probe are computed. The T-Scan ED analyzes the multi-frequency data and produces a binary outcome of negative (normal tissue) or positive (some tissue suspected of being malignant, *i.e.,* suspicious). The device generates data from **[Redacted]** ,which is the default. The device displays nine images per breast (one of each area scanned), which are used to evaluate the quality of the examination, and not the actual breast tissue. Further, a green vertical bar placed between the images of the left and right breasts indicates if there is sufficient contact between the probe and the patient's skin.

The measured conductivity and capacitance values for each sector and for each frequency are averaged over all sector pixels. The set of resulting averages is analyzed by an EIS algorithm that was developed based on data from a subset of patients in the pilot study, which is summarized below in Section 11. The device displays, underneath the illustration of both breasts, a green solid horizontal line if the result is negative or a red hatched line if the result is positive. The device automatically and unambiguously indicates whether the tissue is normal or suspicious. The technology presents no known risk.

The T-Scan ED, in combination with CBE, helps identify young women who are more likely than the normal population to have breast cancer but for whom no other good early detection modality exists. However, the T-Scan ED does not show or identify the location of any suspicious lesion within the breast. A woman who is T-Scan™ positive should be referred for breast imaging with mammography or ultrasound.

The T-Scan ED is a modification to Mirabel Medical's previously approved T-Scan™ 2000 (P970033). As explained in greater detail below, the T-Scan ED is the same device as the approved T-Scan 2000 except that (1) these devices are indicated for use by different patient populations and they are used at different stages of breast cancer detection; (2) they measure electrical impedance of breast tissue at different frequencies; (3) The T-Scan ED incorporates technological updates and new postprocessing algorithms, which are due primarily to its new indication; and (4) they display different information, which is also due to their different indications.

As explained in more detail in Section 6, all of the changes described in the submission were developed and implemented in accordance with the relevant Mirabel procedures contained in the Quality System Manual. The Quality Management System ("QMS") conforms to FDA's Quality System Regulation, 21 C.F.R. Part 820, and was inspected by the Agency in the course of the pre-PMA approval inspection for the T-Scan 2000 device in 1998. The changes are recorded in the Device History Record and also are implemented and documented in the Device Master Record, as described fully in the Design Dossier section (Section 6) of this submission. The manufacturing process for the Model T-Scan ED version of the device is essentially unchanged from the manufacturing process for the Model T-Scan 2000 version. However, as described in the Manufacturing Dossier section (Section 7) of this PMAS, Mirabel Medical currently is qualifying an alternate manufacturing site for the device.

5.1 Indications

The T-Scan ED is indicated for use as a complement to the clinical breast examination ("CBE") in asymptomatic women ages 30 to 39, inclusive. The device detects tissue-based differences in electrical impedance associated with an increased risk for breast cancer. A positive T-Scan™ result provides physicians with additional information regarding the need for further breast examinations, *e.g.,* mammography or ultrasound.

5.2 Description of Device Functional Components

The T-Scan ED is described in detail below followed by a comparison of this device to the approved T-Scan 2000.

5.2.1 Terms and abbreviations

The following terms are used in the upcoming subsections:

ALTERA	Commercial programmable electronic chip
CDR/W	"CD read-write" device
D/A	"Digital to Analog" converter
I/O	"Input - output." Name for two-way channel
ISA	"Industrial Standard Architecture." Name of standard computer bus
LED	"Light Emitting Diode." Colored indicator lamp
LUT	"Look-UP Table." Buffer in memory with real values and an apparatus for converting them to analog values
MMI	"Man Machine Interface." Screens of the device that establish I/O communication with the user
PC	"Personal Computer"
PCI	"Peripheral Component Interconnection." Standard computer bus and protocol
PM	"Processing Module." Specialized electronic board, designed and built for the T-SCAN 2000
RS232	Protocol for binary data interchange
TRB	"Transmit-Receive Board." Specialized electronic board, designed and built for the T-SCAN ED

5.2.2 General Description of The Device

Two versions of the T-Scan ED are available: a desktop version (the T-Scan 2000ED_d) and a version mounted on a cart (T-Scan 2000 ED_c), which is shown in Figure 1. The two versions are identical except that their on/off switches and the T-Scan 2000 ED_c is supplied with a printer while the printer is optional in the T-Scan 2000ED_{dd}. This

supplement covers both versions of the device, which are available in 115V and 230V models. However, for ease of review, this supplement focuses primarily on the cart version and thus, the "T-Scan ED" name without the desktop and cart designations is used in throughout this supplement.

Figure 1: T-Scan ED.

Figure 2 is a block diagram of the device that shows its primary components. The T-Scan ED's primary components are:

- An isolation transformer (labeled "1" in Figure 2) that isolates surface probe and signal transmitter from the external ground and lines;
- A personal computer ("PC") (labeled "2" in Figure 2), with the Transmit-Receive Board ("TRB") (labeled "3" in Figure 2) inserted in the PCI bus;
- A surface probe (labeled "4" in Figure 2), which is a hand-held, 64-sensor scanner that the operator places in contact with the patient's breast when performing a scan;
- A signal transmitter (labeled "5" in Figure 2), which functions as the reference electrode, is a stainless steel cylinder that the patient holds in her hand;

- PC input/output peripherals, which consist of a monitor, keyboard, and trackball, all of which are mounted on top of the cart, for user convenience. Also available is CDR/W, as a back-up storage medium; and

- A laser printer (labeled "6" in Figure 2).

This device is mounted on a mobile medical cart that consists of a closed cabinet containing the main PC and a user tray on which the keyboard, trackball, and monitor sit. The user tray has external holders for the surface probe, signal transmitter, and gel bottles.

Figure 2: [Redacted].

5.2.2.1 General description of the main components

The isolation transformer provides power to the system and isolates the surface probe and signal transmitter. The main electronic board, which is the TRB, is a PCI card inserted in a PCI slot of the PC.

The PC, monitor, keyboard, trackball, printer, and the CDR/W are standard off-the-shelf computer products. A UPS and isolation transformer have been added to the system in order to ensure compliance with medical electric safety standards. The PC contains proprietary software that controls data acquisition, processing, and display, and allows the operator to examine the data in real time. In addition, the computer stores data so that the operator may review and print the data at a later time.

[Redacted].

The sensors, which receive the voltage signals transmitted through the patient, are located on the surface probe. The **Start**, **Stop**, and **Record** buttons for activating the functions most often used during a typical exam are located on the control panel on the back of the surface probe.

5.2.3 Description of Functional Components

A more detailed description of the functional components is provided next.

5.2.3.1 PC and accessories, operating system

The T-Scan ED system incorporates a commercial PC and accessories. The software is a Win32 application running natively on Windows 2000.

5.2.3.2 Transmit-receive board (TRB)

[Redacted].

Figure 3: [Redacted].

The TRB consists of the following:

- **[Redacted]**.
- **[Redacted]**.
- **[Redacted]**.

5.2.3.3 Surface probe

The surface probe (Figure 4) is a hand-held, sealed plastic unit that the operator places in contact with the patient's breast when performing a scan. The T-Scan ED uses the same surface probe as the T-Scan 2000.

Figure 4: The surface probe.

The back of the probe, which faces the operator, includes a control panel with control buttons and control LEDs, whose functions are identified in Table 1. The operator may perform most of an examination by means of these buttons, without using the keyboard or trackball.

Table 1: Surface probe control buttons

Button label	Activity
START/STOP	Starts or stops the viewing without recording the image
REC	Records the current sector image (according to parameters specified by a preselected protocol).

The front of the surface probe, which is placed on the breast surface during an exam, is shown in the left side of Figure 4. It has an 8 x 8 electrode array, **[Redacted]**.

The total active area of the surface probe is **[Redacted]**. The area of each of the electrodes is **[Redacted]**, and the width of the surrounding **[Redacted]**. Each sensor is attached to an electronic switch (located inside the surface probe housing) that controls whether the sensor acquires data or is inert. In both cases, the electrode is kept at ground potential, and the whole active area forms an equipotential surface.

Figure 5: [Redacted].

The user holds the surface probe by its handle and places his/her fingers around the top of the probe, thereby holding it steady at the desired position on the breast, and applying sufficiently consistent pressure to enable the system to scan correctly. (As explained in more detail below, a green vertical line between the images of the left and right breasts on the T-Scan ED's display indicates whether the pressure on the surface probe is sufficient. The surface probe communicates with the rest of the system by means of a cable, one end of which is permanently attached to the surface probe handle, while the other is connected to the TRB by means of a socket on the cart. The sealed surface probe housing contains all the electronic components that need to be protected from exposure to liquid, gel, or other contaminants. The surface probe has smooth surfaces and corners to protect the patient and the operator during contact with the probe.

5.2.3.4 Signal transmitter

The signal transmitter is a stainless steel cylinder (Figure 6) that is connected to the signal generator ("SG") of the TRB by means of a coaxial cable from the transmitter to the SG outlet socket on the cart panel. The signal generated in the TRB is applied to the patient as she holds the signal transmitter in her hand. The level of the signal and safety issues are detailed in Subsection 5.2.3.5, below.

A commercially available medical conducting gel, which is not supplied with the device, is applied to the signal transmitter, surface probe, and skin. The gel reduces the electrodes contact impedance. The gel also serves to reduce the friction between the surface probe and the skin, thereby allowing the operator to accurately maneuver the surface probe to the desired position on the patient's breast.

Figure 6: The signal transmitter.

5.2.3.5 Current limiting circuit

Hardware and software controls limit the voltage and the resulting current to safe levels. The safety circuit works as follows (*see* Figure 7).

[Redacted].

Figure 7: [Redacted].

5.2.3.6 Compliance with safety regulations

As explained in more detail in Section 9.0, the T-Scan ED complies with IEC 610-2-10, "Particular requirements for the safety of nerve and muscle simulators" and IEC/62/6814, "Appliance with human body contact electrodes—safety requirements for use with medical supervision."

5.2.4 Description of the Software

The T-Scan ED's main software modules are as follows:

- The top-level unit that controls the software modules through the four control units, which are: the main board software; the working mode manager; the database manager; and the data processing module;
- The main board software, which is in the TRB, controls the acquisition and spooling of measured data;
- The Man-Machine Interface ("MMI") manager controls the screen display and messages and interprets the user responses;
- The Database manager—based on Microsoft Access®—manages the introduction of new patients to the database, the writing of

data in the recording, and the extraction of existing patient for user inspection; and

- The Data processing module performs the calculation of capacitance (“C”) and conductance (“G”) values and activates the postprocessing algorithm

Figure 8 shows the device’s software architecture.

Figure 8: [Redacted].

Software documentation is provided in Section 6.3 and in **Appendices 6.5.3, 6.5.4, and 6.5.10**.

5.3 Principles of Operation

5.3.1 Introduction

T-Scan ED emits a low AC voltage on a signal transmitter held by the patient’s hand. Electrical currents are collected by a 64-electrode array of a surface probe that the operator places on the patient’s breast. The electric currents are collected, digitized, and analyzed by the device software, and the resulting outcome is displayed as a solid green or red hatched bar on the screen. Details of the device operation are given next.

5.3.2 Start-up Sequence

On power-up, **[Redacted]**. In the course of these tests, the LEDs on the surface probe light in a certain sequence. If the system is functioning properly, only the “**ON LED”** is lit at the end of the start-up sequence. If an error occurs during start-up, the operator or technician can determine the nature of the problem by observing the LED sequence. See the User Manual and the Service Manual for more detailed instructions. The system then proceeds to check and back up the database tables.

5.3.3 The Scanning Process

To begin a T-Scan ED examination, the operator enters patient identifying information into the system via the keyboard. Next, the operator applies commercially available, conductive (ultrasound) gel to the breast, to the signal transmitter, and to the sensors on the surface probe. The gel reduces the tissue-electrodes contact impedance. The gel also reduces the friction between the surface probe and the skin, which allows the operator to easily move the surface probe on the patients breast. The signal transmitter is held in the patient's hand, and the operator starts scanning the patient's right breast, following pictorial instructions shown on the device's screen (see Figure 9). The screen is divided into two parts. The upper part shows two grids of 3 x 3 sectors, each of which corresponds to a measured sector of the breast. The lower half of the screen shows an illustration of the female chest. Each breast is divided into the 3 x 3 grid. The sector being scanned has a yellow frame around it (the nipple is being scanned in Figure 9). After the device records the data for that sector, a yellow frame appears around the next sector to be scanned in both the upper image and the lower illustration. The pictorial instructions direct the user to move the surface probe to the next sector. The process is repeated for all nine sectors of that breast. Sector localization is not designed to be anatomically precise, but to guide adequate sampling of different breast regions.

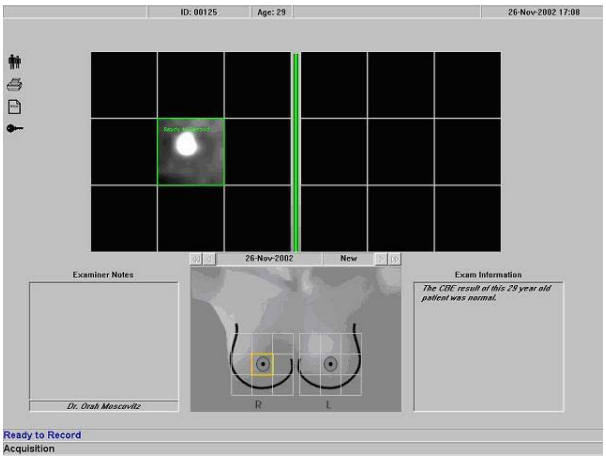


Figure 9: Scan screen. The image shows a successful acquisition of data from the right nipple. Note that the sector image on the top and the corresponding illustrative nipple are circumscribed by frames that guide the operator in the correct positioning of the surface probe.

The scanning process starts from the nipple of the right breast (note that the left breast is on the right and the right breast is on the left as the patient is "facing" the operator.).

The operator scans a sector by pressing the **"Start"** button on surface probe. The system transmits a signal and the surface probe continuously acquires data. The system

processes the data to yield electrical parameters which are shown in real time on the corresponding sector of the image. The images show whether the surface probe is in contact with the entire sector to be scanned. The green vertical bar between the images of the left and right breast indicates whether it is applying sufficient pressure on the surface probe to obtain good data. When the message **"Ready to Record"** apprears in the section to be scanned (see figure 9), the operator presses the **"Record"** button. The system acquires data using a sequence of **[Redacted]**.
The capacitance ("C") and conductivity (G") values are stored. The screen indicates the next sector to be scanned by framing it in yellow. The operator then moves the surface probe to the next sector, and the process is repeated until all nine sectors of the right breast are recorded, which resulting in a complete map of the breast. The same process is repeated for the left breast.

5.3.4 Description of the Measurement Process

[Redacted].

Figure 10: [Redacted].

[Redacted].

Capacitance and conductance values are then calculated from the sampled data: least-square fit is performed on the signal of each pad and on the reference voltage. Values for C and G are obtained from the resulting amplitudes and phases. This process is described further in **Appendix 5.8.2**.

5.4 Properties of the Device Relevant to the Indication of Use

5.4.1 Basics of T-Scan™ Technology

The following is a brief explanation of the Electrical Impedance Scanning ("EIS") technology. Further details can be found in the cited literature (Assenheimer et al. 2001; Jossinet 1996).

Living tissue has a complex, specific electrical impedance (*z*). The inverse of *z* is called "admittivity," (*y*), which can be expressed as the sum of the conductive part *(g)*, and of capacitive component *(c)*:

(1) $$y = g + i \cdot \omega \cdot c$$

These variables (written in italics), which are given in units of Siemens/cm (*y*, *g*) and Farad/cm (*c*), are tissue characteristics that do not depend on the geometry.

When two electrodes are mounted on the tissue and a voltage, ***V***, is applied between them, an electric current, ***I***, flows, and the measured admittance, ***Y***, is defined by Ohm's law:

(2) $$Y = \frac{I}{V}$$

Y is a complex entity that can be expressed as the sum of real and imaginary parts:

(3) $$Y = G + i \cdot \omega \cdot C$$

These variables (written in capitalized font) are given in units of Siemens (Y, G) and Farad (C), and depend on geometry. The G and C in equation 3, and the *g* and *c* in equation 1 have simple one-to-one correspondence only in the ideal case of uniform tissue geometry, mounted between two parallel electrodes, without any contact impedance. However, in any actual use, the electric field-lines are not parallel. Thus, the current *I* represents the sum of subcurrents, each with a different amplitude and phase, flowing through the entire tissue being measured. Also, both the skin and the tissue-electrode contact add serial impedance, which, for frequencies of up to about **[Redacted]**, may be larger than that of the tissue (Woo 1992). As a result, the image generated by T-Scan ED (namely, arrays of C and G values) cannot be used to evaluate the characteristics of the tissue (*c* and *g*). As explained in the next section, the frequency dependence of the measured C and G values enable the T-Scan ED's algorithm to differentiate between tissue, as described in the next section of this study.

5.4.2 Method of Algorithm Development

The T-Scan ED indicates whether the patient's breast tissue is normal or suspicious based on the measured C and G values for both breasts. The C and G values for a total of 18 sectors (9 sectors per breast) are measured with **[Redacted]**.
The measured C and G values for each sector and for each frequency are averaged over all the sector pixels. The set of resulting averages are multiplied by a set of coefficients (denoted "a_i," below) and then added together to obtain the result.

The "core" of the algorithm is the set of coefficients, a_i. The coefficients are evaluated from the electrical data of a learning group by the method of a least square fit, as described further in **Appendix 5.8.3**. The following is a brief summary of the method:

- The C and G values are averaged for each measured sector;
- For each sector and frequency, the averaged C and G are averaged over the population of the learning group. These averages are calculated separately for the cancer group (thus resulting in the vector M(y)) and for the screening group (resulting M(x));
- The covariance matrix D(x) is calculated, for the screening data;
- The difference between averages (M(x)-M(y)) is multiplied by the inverse matrix of D(x). The result is the optimal vector,{a}; and
- Elements of {a} whose values are smaller than predefined threshold are omitted. The resulting vector is the required vector of coefficient, a_i.

The algorithm produces a binary output ("normal" or "suspicious"), which is displayed on the monitor. The device makes this determination by linearly scaling the data into the **[Redacted]** range, and by comparing the result to a threshold value of **[Redacted]**. Values smaller than **[Redacted]** are considered normal, while values equal or greater than **[Redacted]** indicate suspicious for cancer.

The learning, verification, and validation processes and analysis of the algorithm's results are described in **Appendix 5.8.4**.

5.5 Comparison of the T-Scan ED and the T-Scan 2000

5.5.1 General

The T-Scan ED and the PMA-approved T-Scan 2000 (collectively, "T-Scan™ devices"), to which the T-Scan ED is a modification, are real time, noninvasive, radiation free, two-dimensional, multifrequency breast cancer detection devices. The T-Scan ED and the T-Scan 2000 both operate by applying a known voltage signal to the signal transmitter in the patient's contralateral hand, by sampling the voltage and the electric current received

by the detector sensors in the surface probe (which the user applies to the patient's breast), and by processing the voltage samples to calculate the electrical characteristics of the patient's breast tissue. As explained in the next section, the T-Scan ED is indicated for use at a different stage of breast cancer detection, in a different patient population, and primarily physicians with different medical specialties than the T-Scan 2000. However, both devices have very similar technological characteristics and principles of operation. As also explained next in this section, the technological differences between these devices are due primarily to their different indication for use. Section 9 summarizes the preclinical testing conducted on the T-Scan ED to confirm that the modifications do not affect safety or effectiveness of the device. Sections 11 includes clinical data that demonstrate that the T-Scan ED is safe and effective for its proposed indications for use.

5.5.2 Differences in Indications For Use

As noted previously, the T-Scan ED and the T-Scan 2000 are both intended to be used for breast cancer detection, although they have different indications. The T-Scan ED is indicated for use as a complement to a clinical breast examination ("CBE") in asymptomatic women aged 30 to 39, inclusive. The device detects tissue-based differences in electrical impedance associated with an increased risk of breast cancer. A positive T-Scan result provides physicians with additional information regarding the need for further breast examination, *e.g.,* mammography or ultrasound.

The T-Scan 2000 is indicated for use as an adjunct to mammography in patients who have equivocal mammographic findings with ACR BIRADS category 3 or 4. It is not intended to be used in cases with clear mammographic or nonmammographic indication for biopsy. The device provides the radiologist with additional information to guide a biopsy recommendation. As also noted above, the T-Scan ED and T-Scan 2000 have the following differences in their indications: (1) they are complements/adjuncts to different examinations (CBE and mammography, respectively) and thus, they are used at different stages of breast cancer detection; (2) they have different patient populations (asymptomatic women in their thirties without palpable lesions detected by CBE who do not have high risk factors vs. women of any age with equivocal mammograms). In addition, as discussed in more detail below, the T-Scan ED is designed for use primarily by obstetricians and gynecologists, whereas the T-Scan 2000 is designed for use by radiologists.

5.5.3 Differences in Device Components

5.5.3.1 Identical Components

The T-Scan ED uses the same surface probe and signal transmitter as the T-Scan 2000. The T-Scan ED, like the T-Scan 2000, contains the following components:

1. A system cart (cart version only);

2. An isolation transformer;

3. A UPS;

4. A laser printer;

5. A host PC and accessories (keyboard, trackball, screen, back-up device); and

6. The main electronic board **[Redacted]**.

The T-Scan ED incorporates newer versions of these components than the T-Scan 2000.

5.5.4 Differences in Technological Implementation

5.5.4.1 Differences in appearance

As shown in Figure 11, both devices are mounted on medical carts that bear the main PC, the PC accessories (keyboard, trackball, printer), and the screen. T-Scan ED includes a movable mount for the screen. The T-Scan 2000's PC screen is mounted on the top of the system cart. Both systems have external mounts for the surface probe, signal transmitter, and gel bottles.

Figure 11: T-Scan 2000 and T-Scan ED

5.5.4.2 Differences in interfacing the main board

The T-Scan ED has an integrated PCI card, mounted on the computer's PCI slot, and the device makes all the communication through the computer PCI bus. The T-Scan 2000 transfers control commands through an RS232 serial connection, and the surface probe

data to the parallel port through a fast ISA I/O card. These differences are summarized in Table 2.

Table 2: Interfaces of the two versions

Parameter	T-Scan 2000	T-Scan ED
Type of main board	Stand-alone	PCI card
Interface to command unit	RS232 on serial port	PCI bus
Data interface	Parallel port to fast ISA I/O card	PCI bus

5.5.4.3 Differences in transmission characteristics

The T-Scan ED's frequency transmission range is **[Redacted]**.
[Redacted]. **[Redacted]** data provides a high contrast between G and C values in the lesion area and the surrounding tissue, and, thus, the operator can identify, by visual inspection, suspicious areas on the image. Higher frequencies have more differentiating power in "average" parameters because the algorithm uses mathematical averages, and ignores the internal variations inside the sector. **[Redacted]**.

[Redacted].

Table 3 summarizes the differences between the two devices' transmission capabilities.

Table 3: [Redacted].

5.5.4.4 Differences in software

Software of both systems has the same general architecture (described previously in Section 5.2.4). The differences between the two device's software are described in Table 4.

Table 4: Differences between T-SCAN 2000 and T-SCAN ED software

Component	T-SCAN 2000	T-SCAN ED
Operating system	Windows NT 4.0	Windows 2000
Architecture	Win 16	Win 32
Programming language	C++	Visual C++
Database infrastructure	Microsoft FoxPro®	Microsoft Access®
Interface to main board	Data transfer: RS232 protocol through the serial port. Commands: the parallel port	PCI bus
On-line utilities	Real-time display of conductance and capacitances	Real-time display of conductance. "Dynamic bar" indicates recording quality. Recording is allowed only for eligible data.
Gail Calculator	Not available	Calculator included

The Gail model (Gail 1989) is a well published breast cancer risk calculator. The T-Scan ED includes a Gail calculator, but its use is optional. The calculator uses the patient's bio-clinical data and evaluates five-year and lifetime cancer expectancy. The T-Scan ED's Gail calculator results were verified by comparison to published Gail values in NCI reports. The verification protocol for the Gail calculator, which is performed on every released software version, is provided in **Appendix 5.8.5**. The T-Scan ED's results are independent of that calculation. It should be noted that the Gail model is provided for physicians who want to offer Gail data to patients. Gail data is not associated with the EIS exam or EIS results in any manner.

5.5.4.5 Difference in algorithm

No specific areas of suspicion in the breast have been identified in the T-Scan ED's patients before the examination. Therefore, this device scans the whole breast area and uses algorithms that compare its electrical properties to the electrical properties of cancerous and normal breast tissue derived from the general population. A description of the T-Scan ED's algorithm is provided in **Appendix 5.8.3.** On the other hand, the T-Scan 2000 was designed to provide additional information about a specific equivocal area of suspicion identified by mammography. For this reason, the device uses an algorithm that compares the electrical properties within the suspected area. A more detailed description of the T-Scan 2000's algorithm is provided in **Appendix 5.8.6**. Both systems analyze electrical parameters of the breast and provide the user with information regarding whether the tissue is suspicious for cancer. The differences between the algorithms are summarized in Table 5.

Table 5: Difference between the algorithms of T-Scan 2000 and T-SCAN ED

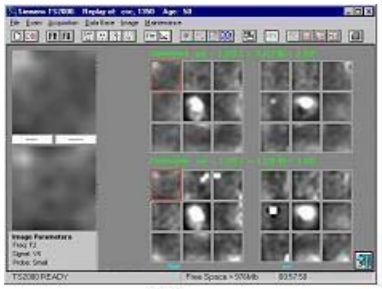
Parameter	T-Scan 2000	T-Scan ED
Electrical input parameters	Images of C, G at **[Redacted]**, phase at the selected frequency (P1), average of phases over the whole spectrum (P2)	**[Redacted]**
Normalization/working point	Center and width of the display window, tuned to provide high sensitivity to nonuniformities on the image	Threshold is factory set to provide the required high specificity
Method	User identifies abnormalities ("spots") on the image	Device indicates whether the tissue is normal or suspicious by means of a colored bar
Verification/Validation	Tested on validation data	Algorithm was tested on test groups, sensitivity and specificity found within the confidence intervals of the learning group (see **Appendix 5.8.4**)

5.5.4.6 Differences in the scan screen

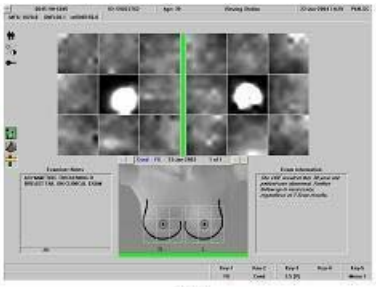
The T-Scan ED, like the T-Scan 2000, measures conductivity and capacitance over nine sectors of each breast, but the devices measure these parameters at different frequencies **[Redacted]**. The devices show images of both breasts simultaneously, with the right breast on the left side and left breast on the right side of the image.

The T-Scan 2000's screen, which is shown in Figure 12A, displays both a conductivity (top) and a capacitance (bottom) image for each of the nine sectors, and, thus, a total of 18 images per breast. The sensitivity of detection of this device depends on its "windowing" which means the range of values that is actually transformed into gray scale on the screen. Values below that range are shown in black, while values above it are shown in white. If the suspicious "spot" (image abnormality) and the background values both fall in the gray scale, the user is able to differentiate between them. On the other hand, if the values fall below or above the gray scale, both have the same appearance and the user cannot identify the suspicious spot. Therefore, the windowing of the T-Scan 2000 influences the ability of the device to differentiate among tissue. A suspicious area is indicated by a bright spot, as seen in the left center sector of the breast on the right in Figure 12A. The detection is based on visual interpretation of such hot spots, *i.e.,* image nonuniformities in the displayed electrical parameter. A larger color picture of the T-Scan 2000's screen is provided in **Appendix 5.8.7**.

The T-Scan ED's screen shows only the conductivity image for each sector (*see* Figure 12B). These images are used only to evaluate the quality of the recording and not for identifying suspicious areas. The green vertical line between the images of the breasts, which is called the "dynamic bar," also indicates the quality of the recording (the higher the bar, the better the quality). In addition, the T-Scan ED displays a solid green or red hatched horizontal line beneath the diagram of both breasts, which indicates whether the tissue is normal (green), as shown in that figure, or suspicious (red). The pattern in this bar allows people who are color-blind to determine whether the bar is red or green. The bar is either green or red; there is no gradation of color between them. Larger color pictures of the T-Scan ED's screen are provided in **Appendix 5.8.8**. The first picture shows a green horizontal line beneath the illustration of the breasts which indicates a positive T-Scan ED examination. The second picture shows a red hatched line beneath the illustration of the breasts which indicates a negative T-Scan ED examination.



12A



12B

Figure 12A: Images of T-Scan 2000, and Figure 12B: T-Scan ED

The T-Scan ED, unlike the T-Scan 2000, does not show where the suspicious tissue is in the breast or whether it is in the left or right breast. However, the T-Scan ED automatically generates a definitive result (normal or suspicious), while the user of the T-Scan 2000 must make the determination by analyzing and interpreting the images. The labeling for both devices states that the clinician should consider recommending any patient with suspicious results for further breast evaluation, although women with positive T-Scan 2000ED results generally are referred to mammography or ultrasound, the prior T-Scan 2000 device was used to refer positive women to biopsy.

5.5.5 Difference in Intended Users

T-Scan 2000 is intended to be used by radiologists, who are trained to detect and interpret "hot spots" on mammographic films and ultrasound images. For this reason, the T-Scan 2000 is designed to produce breast images that require hot-spot detection and interpretation. On the other hand, T-Scan ED is intended to be used primarily by primary care physicians. Therefore, the T-Scan ED is designed to indicate whether the tissue is normal or suspicious, rather than to produce an image that requires hot-spot detection and interpretation. A table comparing the T-Scan ED to T-Scan 2000 is provided in Table 7 below:

Table 7. Principal Differences between the T-SCAN 2000 and T-Scan ED

	T-Scan 2000	T-Scan ED
Indications	Adjunct to mammography in patients who have equivocal mammographic findings within ACR BI-RADS categories 3 or 4. It is not intended for use in cases with clear mammographic or nonmammographic indications for biopsy. This device provides the radiologist with additional information to guide a biopsy recommendation.	The T-Scan ED is indicated for use as a complement to clinical breast examination ("CBE") in women age 30 to 39, inclusive, who do not have any palpable lesions detected by CBE or a family history of, or genetic risk factors for, breast cancer. The device detects differences in the electrical impedance of tissue that are associated with an increased risk of breast cancer. A positive T-Scan™ result provides physicians (primarily obstetricians and gynecologists) with additional information to guide a recommendation regarding further breast examination, e.g., mammography, magnetic resonance imaging, or ultrasound
Intended patient population	Women of any age who have an equivocal mammogram	Women younger than the minimum age currently recommended for annual screening mammography who do not have a palpable breast lesion or a family history of, or genetic risk factors for, breast cancer
Information provided by the device	Conductance and capacitance images of the breasts	Conductance images of the breast and a diagram of the breasts with a green or red horizontal line under it indicating whether the tissue is negative (normal) or (positive) suspicious
Use of Images	Clinical decision	To evaluate the quality of the recorded data. The images are not used for a clinical decision

	T-Scan 2000	T-Scan ED
Information provided	Evaluation of a specific lesion	Conclusion about whether the tissue is negative (normal) or positive (suspicious)
Frequencies	**[Redacted]**	**[Redacted]**
Duration of Procedure	Approximately 15 minutes	Approximately six minutes
Assurance of recording quality	Visual inspection of the image on the screen	Visual inspection of the image on the screen and dynamic vertical bar
Method of scoring	User identifies abnormalities in the impedance maps	Algorithm evaluates multi-frequency impedance parameters and determines whether the women is at higher risk for breast cancer than the general population
Gail scale	Not available	Calculator included

5.6 Conclusion

In summary, Mirabel Medical's T-Scan ED is a modification to Mirabel Medical's PMA-approved T-Scan 2000. Both devices are intended to be used for breast cancer detection and to provide clinicians with additional information on which to base a recommendation regarding further breast examination. However, the T-Scan ED is indicated for use in asymptomatic women in their thirties while the T-Scan 2000 is indicated for women of any age who have equivocal mammograms. As a result, these devices have different patient populations and they are used at different stages of breast cancer detection. In addition, these devices are designed to be used by clinicians with different medical specialties: primary care physicians, obstetricians and gynecologists are intended to be the primary users of the T-Scan ED because this examination is intended to be performed immediately after CBEs, while the T-Scan 2000 is intended to be used by radiologists to provide them with additional information to interpret equivocal mammograms.

The T-Scan ED and the T-Scan 2000 use electrical impedance scanning to detect suspicious breast tissue. The T-Scan ED has the same primary components as the T-Scan 2000 (Surface Probe and Signal Transmitter) and its other components are versions of the approved device's components. The T-Scan ED and the T-Scan 2000

examinations both involve scanning given sections on each breast The differences in their technological characteristics, other than computer hardware and software upgrades and advances in cart technology since the approval of the original device, are (1) the frequencies at which they sample the conductivity and capacitance of the tissue **[Redacted]**; (2) the T-Scan 2000 displays 18 images per breast (nine each for conductance and capacitance), while the T-Scan ED displays only nine images per breast (conductance only); (3) the T-Scan ED's dynamic bar that indicates the quality of the data, which is in addition to the clinician's visual evaluation of the quality of the images displayed by both devices; and (4) the T-Scan ED indicates by means of a green or red bar whether the tissue is normal or suspicious for breast cancer while the user must analyze the images displayed by the T-Scan 2000 (especially the equivocal area identified by the mammography) to make that decision. These differences, which are achieved primarily through the T-Scan ED's modified postprocessing algorithms, are due to these devices' different breast cancer detection indications.

The verification and validation testing of the T-Scan ED's modified algorithm, which is summarized in the software documentation provided in **Appendix 6.5.3** of this PMAS, confirms that the T-Scan ED functions as intended. The clinical data summarized in Section 11 of this PMAS, including data from a prospective, multicenter clinical study, shows that the T-Scan ED is safe and effective for its proposed indication.

5.7 Draft Labeling

The draft labeling for the T-Scan ED consists of the device labels, a user's manual, information for prescribers, promotional material, a patient guide (in question-and-answer format), and a service operation manual. The draft device labels are provided in **Appendix 5.8.9**. The draft User's Manual is provided in **Appendix 5.8.10**. The "Information for Prescribers" is provided in **Appendix 5.8.11**. The draft Patient Guide, which is in the form of questions and answers, is provided in **Appendix 5.8.12**. The draft Service Manual is provided in **Appendix 5.8.13**. The draft promotional material is provided in **Appendix 5.8.14.** The same draft labeling is appended to Section 13.0 of this PMAS, which is entitled "Labeling." The draft labeling is provided in this section for FDA's convenience.

5.8 Appendices

APPENDIX 5.8.1 Safety Tests

APPENDIX 5.8.2 Description of the Measurement Process

APPENDIX 5.8.3 Algorithm of the T-Scan ED

APPENDIX 5.8.4 Verification and Validation of the T-Scan ED

APPENDIX 5.8.5 Gail Calculator Test

APPENDIX 5.8.6 Algorithm of the T-Scan 2000

APPENDIX 5.8.7 Color Picture of the T-Scan 2000's Screen

APPENDIX 5.8.8 Color Picture of the T-Scan ED's Screen

APPENDIX 5.8.9 Device Labels

APPENDIX 5.8.10 User's Manual

APPENDIX 5.8.11 Information for Prescribers

APPENDIX 5.8.12 Patient Guide

APPENDIX 5.8.13 Service Manual

APPENDIX 5.8.14 Promotional Material

Mirabel
MEDICAL SYSTEMS

December 12, 2005

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

Attention: Robert A. Phillips, Ph.D. (HFZ-470)
Re: Mirabel Medical Inc., T-Scan 2000 ED, P050003

Amendment to the Premarket Approval Application for
The T-Scan™ 2000 ED Breast Cancer Risk Screening System

Dear Dr. Phillips:

Enclosed for FDA's review, please find an update of "Section 11 - Clinical Studies" that incorporates additional data collected since the initial submission of the Premarket Approval Application ("PMA" P050003) for the T-Scan™ 2000 ED.

As requested by Dr. Donna-Bea Tillman and the Branch, this amendment incorporates additional Sensitivity Arm data from 108 exams and 19 cancers that have been collected, monitored and analyzed since the original PMA submission. Additionally, as previously submitted in Amendment 1 (July 26, 2005), all calculations in this amendment include the updated device specificity with the minor change from 94.9% to 94.7% specificity.

For your convenience, Table1 below summarizes the additional data provided in this amendment and presents results for the primary study endpoint of relative and absolute risk for breast cancer in T-Scan positive patients. These additional data further support the previous conclusions of the pivotal trial, namely; that the device is safe and effective for its intended use as a compliment to clinical breast examination in

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asymptomatic women age 30-39 for detecting differences in the electrical impedance of tissue that are associated with an increased risk of breast cancer. A positive T-Scan result does not confirm the presence of cancer; rather it provides physicians with additional risk information to guide a recommendation regarding the need for supplementary breast examination, *e.g.*, mammography or ultrasound.

Table 1 Relative and absolute risk for breast cancer (amended) compared to study threshold and baseline patient populations

Patient Population	Relative Risk for Breast Cancer (95% CI)	Absolute Risk for Breast Cancer	
Pivotal Study Results, Amended (87 cancers, 1751 benign)	4.95 (3.16,7.14)	1:136	0.0073
Patient with first degree relative having breast cancer ("study threshold")	2.0	1:333	0.0030
Average risk women, 30-39	1.0	1:667	0.0015
Average risk women, 40-50	1.0	1:400	0.0025

As can be seen from the table above, women who test positive on the T-Scan exam are at a breast cancer risk that is **4.95** times greater than their peers and have an absolute risk for breast cancer that is considerably greater than the risk associated with a positive family history of breast cancer. Perhaps most importantly, the absolute risk for breast cancer in T-Scan positive women is nearly three times greater (.0073 vs. .0025) than that of women age 40-50, who are routinely offered screening mammography. Thus, T-Scan is highly effective as a means for pre-screening average risk, pre-menopausal women and identifying those who are at considerably elevated risk for breast cancer and should consider further imaging prior to the standard initiation of mammography at age 40.

To quote a review article titled "Assessing the Risk of Breast Cancer" published in the *New England Journal of Medicine*, "The assessment of breast cancer risk cannot improve the efficacy of mammography, but targeting mammography to women at higher risk of breast cancer can improve the balance of risks and benefits. Among women at higher risk, mammography results in a greater absolute decrease in the risk of death from breast cancer and is more cost effective."[1]

[1] Armstrong K, Eisen A, Weber B. Assessing the risk of breast cancer. N Engl J Med 2000; 564-571

Since only about 10% of women diagnosed with breast cancer have a known prior family history of the disease, the availability of the T-Scan 2000 ED represents a clinically-meaningful and broadly-applicable opportunity for the timely identification of young women who are most likely to benefit from earlier screening with mammography or ultrasound.

We very much appreciate your willingness to review this amendment and look forward to your response. As always, if you have any questions regarding this submission, please do not hesitate to contact me by phone at (512) 338-9090 or by fax at (512) 338-9393.

Sincerely,

Ron Ginor, M.D
President & CEO

Attachments:

- PMA Section 11 – Clinical Studies (amended)
- Tabulated Data Listing (amended)

cc: Kishalaya Chakrabarti, Ph.D.
Donna-Bea Tillman, Ph.D.
Ron Yustein, M.D.

11. Clinical Studies

11.1 Introduction

11.1.1 Background

Breast cancer is the most commonly diagnosed non-skin malignancy and the second leading cause of cancer death in women. Despite the low absolute risk of the disease in women under the age of 40 (about 1.5-2.0/1000 women, Kerlikowske *et al*., 1993), breast cancer is the leading cause of cancer death in all women aged 15-34 (National Cancer Institute, Fact Book, 2003) and incidence is increasing in this age group specifically (Kopans, 1998). For these reasons, a growing emphasis is being placed upon the need for earlier detection and potentially prevention in this age group. However, due to the inherent limitations of mammography in younger women, current screening guidelines do not recommend routine mammographic screening for average-risk women before the age of 40. Consequently, the incidence of breast cancer in younger women is probably underestimated, as many cancers developing among women in their thirties are not discovered until they have their first screening mammogram at age 40. This hypothesis is supported by the higher rate of cancer detection with the first mammogram as compared to all subsequent mammograms (Kopans, 1998).

Breast cancer, when it does occur in young women, tends to be more aggressive than in older women (Peer *et al*., 1996; Fisher *et al*., 1997; Kopans, 1998; Xiong *et al*., 2001; Dubsky *et al*., 2002; Love *et al*., 2002) and, consequently, its early detection may be of particular importance. The more aggressive nature of breast cancer in young women indicates that screening could have a greater impact in reducing mortality in this cohort if it were conducted at shorter intervals (Feig, 1995). Additionally, the costs of missed breast cancer in this group are particularly high. Aside from the direct economic and emotional costs, the significant detriment in terms of life-years lost is especially substantial in young women. Specifically, it is estimated that approximately 40% of life years lost to breast cancer are lost in women who die in their forties (Kopans, 1998).

Mammography is commonly regarded as the single most important advance in the early detection of breast cancer. Mammography, however, is not generally recommended for women under the age of 40 for a number of reasons, including cost, radiation exposure and limited access. Perhaps the principal limitation of mammography in young women is that screening mammography suffers from significantly lower sensitivity in dense breasts, which typifies the breast tissue of virtually all women under age 40. According to some studies, standard screening mammography may, in fact, be less than half as sensitive in dense breasts (Berg *et al*., 2004). Thus, only patients who are "at risk" due to a family history and/or genetic factors (BRCA gene carriers), are encouraged to start annual mammographic screening under age 40. While increased surveillance for "at risk" women appears beneficial (Johnson *et al*., 2002; Kollias *et al*., 1998; Tilanus-Lindhorst *et al*., 2000), the categorical value of this screening paradigm is significantly limited by the fact that known genetic risk factors are rare and "are estimated to account for no more than 5% to 10% of breast cancer cases overall" (Hall *et al*., 2001, Johnson *et al*., 1995, Pharoah *et al*., 2000). Accordingly,

even if all patients with known genetic risk factors were offered an effective regimen of screening and prevention, the data suggest that 90-95% of breast cancers would occur in patients who do not have genetic risk factors and as such would not be offered the potential benefit of increased surveillance. It therefore stands to reason that technologies which offer additional methods for identifying risk, based on specific, individual tissue factors, as opposed to more generalized statistical or familial risk factors, may present an important opportunity to risk-stratify and preferentially screen a large and previously unscreened population of "at risk" women.

Electrical impedance based technologies, owing to their non-invasive nature and suitability for use in dense breast tissue (Malich *et al*., 2000), may be useful in identifying specific tissue characteristics that are associated with an increased probability for breast cancer. Significant differences in electrical impedance properties between malignant and normal tissue have been extensively published in a series of *in-vitro* measurements on freshly excised breast tissue (Fricke and Morse, 1926; Jossinet, 1996, 1998; Morimoto *et al.,* 1990; Suroweic *et al*., 1988).

The T-Scan™ 2000ED ("T-Scan ED") is a noninvasive and radiation-free Electrical Impedance Scanning (EIS) device developed to address the specific epidemiological and physiological requirements associated with primary breast cancer screening of young women. Specifically, the device maps and analyzes the local impedance properties of breast tissue (Assenheimer *et al*, 2001; Scholtz and Anderson, 2000) and identifies electrical impedance parameters that are associated with neoplastic activity.

The initial development of T-Scan ED technology was conducted during the evaluation of the predecessor device ("T-Scan 2000"), which received FDA approval in April, 1999 (PMA P970033). The T-Scan ED version, subject of this PMAS, is a modified version of the original T-Scan 2000 using the same measurement technique, patient interface and electrical current levels but incorporating a software algorithm which utilizes different thresholds and operates at a different point on the ROC curve. Thus, the T-Scan ED offers a ratio of sensitivity and specificity which is consistent with a **screening** tool – as opposed to the very high sensitivity and moderate specificity of the prior T-Scan 2000 – which is a **diagnostic** tool.

Two clinical studies have been conducted to evaluate the clinical safety and effectiveness of the T-Scan ED. An initial pilot study, summarized below, was conducted in 2002-2003 in order to evaluate the feasibility of combining a post-processing algorithm with the core EIS technology. A second, pivotal, trial was developed with input from FDA in order to provide reliable estimates of sensitivity and specificity and, in turn, estimate the device's ability to detect tissue changes and identify breast cancer risk in the target population. Based upon the current standard of care, whereby women with a relative risk of 2.0 or more are considered "at risk" and offered additional imaging, greater surveillance and enrollment in specific management protocols (Kramer and Brown, 2004; Pharoah *et al*., 2000; Tilanus-Lindhorst *et al* 2000), the FDA, clinical investigators and the Company agreed that a positive T-Scan ED result would need to reflect a risk of 2.0 or more to be clinically useful. Thus the primary endpoint of the pivotal study was to determine if a woman who is positive on a T-Scan ED exam is at a risk for breast cancer that is at least two times greater than the expected risk in the general target population. This study is described in detail below.

11.1.2 Pilot Study

11.1.2.1 Rationale

The FDA-approved predecessor device (T-Scan 2000) identified cancers by creating impedance maps of the breast and displaying white focal areas, consistent with regions of atypical flow, on the EIS image. This method of imaging, however, was susceptible to significant inter-operator variability, and as such, offered good sensitivity but a level of specificity that was highly dependant on operator experience with the technology (Piperno *et al*., 1990; Melloul *et al*., 1999; Malich *et al*., 2000, 2001).

The advent of computer-aided detection (CAD) software in mammography and other areas presented an opportunity for the standardization of EIS images as well. In 2001, the company set about developing an algorithm to automatically analyze the EIS image in the T-Scan 2000 and present a binary "negative" or "positive" result in a manner that is consistent across users (Glickman *et al*., 2002). Notably, the development of this algorithm also made it possible to set different thresholds for a negative or positive result.

Thus, different working points on the ROC curve could be utilized for different purposes and screening populations. For example, when used as an adjunctive modality to mammography for the purpose of ruling out biopsy, the algorithm thresholds were set so as to have very high sensitivity and moderate specificity (Kolb *et al*., 2002, Fuchsjaeger *et al*., 2002). However, the algorithm could also be modified to yield a high level of specificity with an associated lower level of sensitivity as appropriate for screening a low-risk population such as young women. This approach for screening younger women with a low cost, low risk, high specificity device having moderate sensitivity was emphasized by the National Academy of Sciences in their Report, Mammography and Beyond (National Academy of Sciences, 2001).

It was this high specificity/low sensitivity modified algorithm P that was initially tested in the Pilot Study with the expectation that if a modified algorithm could significantly elevate specificity, which was traditionally low with EIS technologies, further developments for improving sensitivity, especially through the use of higher frequencies, would be warranted.

11.1.2.2 Methods

Pilot data were collected using the experimental algorithm P. The purpose of this pilot study was:

- To determine if the core EIS technology, coupled with an experimental processing algorithm could achieve a high (>90%) level of specificity.
- To collect data for further development of an algorithm offering high specificity and clinically useful sensitivity incorporating higher frequency recordings. **[Redacted]**.

Following IRB approval, pilot data were collected at 14 medical centers on a total of 1,708 women ranging in age from 17-77 years. Clinical sites included:

[Redacted].

Patients presenting at the medical center for screening mammography, ultrasound, annual gynecological exam or for breast biopsy were offered enrollment in the study. Apart from allowing a technologist to perform a T-Scan™ exam prior to their scheduled appointment or procedure, patients who enrolled in the T-Scan™ study followed their regular clinical course regardless of T-Scan™ result.

Sensitivity of the device was estimated by comparing the rate of T-Scan™ positive results with the number of biopsy proven cancers. Specificity was evaluated based on the assumption that women did not have breast cancer if:

- they were normal on all other performed screening examinations (CBE, US and/or mammography);
- they had lesions that were not deemed sufficiently suspicious to warrant biopsy; or
- they had biopsy-proven benign lesions.

The above assumptions are supported by the expected low prevalence of disease and the reliance on currently accepted gold-standard exams for confirmation of health or disease.

All T-Scan™ examinations were performed prospectively (prior to biopsy, if any). Hence, the examiner was blinded as to the actual histological diagnosis. In addition to collecting results of the EIS examination and all other breast studies for each patient, data were also collected on menopausal status, use of exogenous estrogen hormones, family history and previous history of breast cancer.

11.1.2.3 Results

SENSITIVITY/SPECIFICITY

Women without cancer were classified in one of two clinical categories:

- Screening cases – These "clinically benign" cases consist of asymptomatic women who had a routine, normal CBE and women who had scheduled routine screening with mammography or ultrasound that showed no evidence of breast cancer. This category also includes women who had a breast finding that was considered benign by the examining physician and thus did not warrant biopsy or further evaluation.
- Benign cases – These "histologically benign" subjects consist of cases where the patient underwent biopsy based on CBE and/or an imaging study, and the mass was found to be histologically benign.

Women found to have cancer based on the pathology report were classified in the following category:

- Cancer Cases – these cases were reported to have biopsy confirmed breast cancer on histological evaluation of the breast specimen.

Sensitivity and specificity for various clinical categories are shown in Table 11.1 below.

Table 11.1 Specificity and sensitivity (Pilot Study)

	N	Specificity 95% CI
Screening Cases	1352	92.6% +/- 0.01%
Benign/Biopsy Cases	295	93.9% +/- 0.03%
Total non-cancer	1647	92.8% +/- 0.01%
	N	**Sensitivity 95% CI**
Cancer Cases	61	11.5% +/- 0.08%

Using logistic regression, there was no significant relationship between specificity and presence or absence of a palpable lesion (p=0.12**)** or patient age (p=0.81). Palpability and age also did not reach statistical significance (p=0.40 and p=0.80, respectively).

Lesion size data, preferentially determined by biopsy, were available for 52 of the 61 carcinomas. If no biopsy data were available, lesion size was based on ultrasound or mammography in that order (except for cancers present solely on mammography as microcalcifications). Finally, when no size data were available from any imaging modality, size was determined by the recorded size for palpation.

Sensitivity tended to be higher for small ($\leq$10 mm) lesions (18.8% (3/16) than for larger (>10mm) lesions 8.3% (3/36). The smallest cancer detected by EIS in this study was 7 mm in size.

Findings of increased sensitivity for sub-centimeter lesions were not statistically significant ($\chi 2=1.18$, $p=0.28$), but the trend for increased sensitivity in small lesions is consistent with prior EIS studies using the approved T-Scan 2000 (Kolb *et al*., 2002, Fuchsjaeger *et al*., 2002; Wersebe *et al*., 2002). For example, in a study of 260 biopsy-proven lesions including 70 cancers (Kolb *et al*., 2002), sensitivity was 100% for 29 small cancers ($\leq$ 10mm in size) and only 79% for 28 larger cancers ($p=0.008$; chi-square).

11.1.2.4 Conclusion from the Pilot Study

Data from the pilot study indicated that it was indeed possible to construct an EIS algorithm that could consistently operate at a level of very high specificity. However, as expected, shifting to an area of very high specificity on the ROC curve had the associated impact of lowering sensitivity.

In order to operate at a level of high specificity while maintaining a clinically beneficial rate of sensitivity, additional electrical impedance characteristics, measured at higher frequencies, were considered for incorporation into the final clinical algorithm.

Specifically, it was determined that an improved algorithm could be constructed by incorporating the high-specificity thresholds in the experimental algorithm combined with additional lesion characteristics measured at higher frequencies **[Redacted]**. This initial determination was based upon a significant body of literature (reviewed in Scholtz and Anderson, 2000) indicating that high frequency EIS measurements are of specific value in the assessment of complex lesions.

Using data from the pilot study, a sub-analysis looking at the high-frequency data was performed on a cohort of patients under the age of 46. Results of this analysis indicated that the combination of higher frequencies with a high-specificity post-processing algorithm may be of specific value in isolating small (sub-2cm lesions) in a background of dense breast tissue.

The assimilation of clinical and physical factors, as described above, formed the basis of the EISYS algorithm, the development of which is more extensively detailed in Section 5 of this PMAS application.

The EISYS algorithm, which is at the core of the T-Scan ED, held specific promise in the detection of small to medium lesions in dense breast tissue. From a clinical perspective, this combination of factors appeared consistent with the epidemiological and statistical requirements set forth by the Institutes of Medicine ("IOM") in regards to the development of improved technologies for breast cancer detection in younger women (Mammography and Beyond, National Academy of Sciences, 2001).

Thus, Company approached the FDA in April, 2003 with the intention of conducting a multi-center pivotal study evaluating the potential role of the T-Scan ED system in detecting early signs of breast cancer in a target population of younger women who would otherwise be screened with manual breast exam alone. This study is discussed in detail below.

11.2 Pivotal Study

11.2.1 Overview

Because the experimental algorithm showed specific promise in accurately identifying a population of young women at increased risk for breast cancer, a larger, pivotal, multicenter study was designed to specifically evaluate the association between T-Scan™ positivity and breast cancer risk in a target population of young women. The pivotal study, described below, provides the primary clinical data in this PMA Supplement supporting the safety and efficacy of the T-Scan ED when used as a primary screening modality for breast cancer risk stratification in women aged 30-39.

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 ED. All per-protocol cases included in the Specificity Arm of this study were in the intended use population of women age 30-39. In the Sensitivity Arm, however, an enriched population (pre-biopsy, expanded age range (30-45) and palpable lesions) was accepted by FDA in order to allow more expeditious accrual of patients while maintaining breast tissue characteristics that are consistent with the target population. By expanding the age range to 45 in the Sensitivity Arm, the study benefited from the inclusion of patients in a higher prevalence group who are scheduled for biopsy based upon a prior clinical finding. However, by not enrolling patients above age 45 and excluding patients who were post-menopausal, the study ensured that the device was used in women who had breast tissue consistent with women in the intended use population.

The primary endpoint of the study entailed using these estimates of sensitivity and specificity to calculate "relative probability," that is, the probability that a woman who is T-Scan™ positive has cancer relative to a randomly selected woman from the population at large using the formula below:

$$P_r = \frac{S_n}{S_n R_{ca} + (1-Sp)(1- R_{ca})} \qquad \text{(Formula 11.1)}$$

Relative probability is a function of the sensitivity (S_n), specificity (S_p), and the prevalence of cancer in the population (R_{ca}).

This study was designed as a multicenter, prospective study. Because of the two-armed nature of the study, the summary of protocol and results are described separately for the Specificity and Sensitivity Arms. Some information is identical in both arms and this information is presented in the Specificity Arm Summary of Protocol section and indicated as being identical in the Sensitivity Arm Summary of Protocol section.

After the discussion of the protocol and results for each arm of the study, the final study outcome measure of relative probability is presented based on data from both arms of the study.

Finally, the risks and benefits posed by the T-Scan ED are discussed.

11.2.2 Specificity Arm

11.2.2.1 Summary of Protocol

Below is a summary of the protocol for the Specificity Arm of the two-arm study. The entire protocol, as reviewed by FDA, is attached to the complete PMA application as **Appendix 11.6.1.**

Study subjects in this arm of the study consisted of women ages 30-39, inclusive, who had no breast related signs or symptoms and who visited their OB/GYN or breast center for an annual physical exam.

All patients who met the inclusion criteria and who were willing to take part in the study were introduced to the technology, consented and examined (scanned) with the T-Scan ED device.

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

Because all women were young and had a negative clinical breast exam, it was assumed, for the purposes of this study, that ***all*** women in the Specificity Arm of the study were free of breast cancer.

Importantly, all patients included in this arm of the study continued with their standard course of clinical care. Negative T-Scan™ results were not taken into clinical consideration in the management of patients in either arm of the study.

Therefore, for purposes of this arm of the study:

- Any positive T-Scan™ exam was considered a false positive, and
- Any negative T-Scan™ was considered a true negative.

Women were also questioned regarding potential covariates such as hormone use, brassiere size, and family history of breast cancer.

Cases were to be collected until there were data on at least 1,500 women without palpable lesions (1,000 from sites in the United States and 500 from international sites).

CLINICAL SITES

The T-Scan ED study's Specificity Arm was conducted in a total of 17 clinical sites. Clinical investigators and monitors were chosen in accordance with the principles set forth in 21 CFR 812. All study sites selected for participation in the study had:

- an active gynecological or breast screening practice consisting of a large number of young female patients,
- an expressed interest in new diagnostic modalities, and
- previous participation in clinical research such that the investigators were familiar with the required procedures and concepts.

Each site designated an investigatory staff that included:

- at least one Site Coordinator (usually the Principal Investigator, or another clinician) with overall responsibility for the proper implementation of the protocol at the site,
- at least one Examiner (clinician or non-clinician) who was responsible for conducting the examinations, and
- a Data Manager with full responsibility for gathering data and entering it in the appropriate case report forms.

The examiners at all participating centers were trained by Mirabel Medical staff and taught how to appropriately perform T-Scan™ examinations, evaluate patients for eligibility per the protocol and complete and maintain the CRFs.

PATIENT ELIGIBILITY

Patients between 30 and 39 years old visiting their gynecologist or breast center for an annual physical exam were eligible for inclusion in the study. Potential subjects were then evaluated against study inclusion and exclusion criteria as outlined in the protocol. Patients meeting the inclusion criteria were considered enrolled in the study upon signing the informed consent. No patient was withdrawn from the study unless the patient withdrew consent before treatment or no T-Scan™ evaluation was ever attempted.

INCLUSION CRITERIA

Prior to enrollment in the Specificity Arm of the study, candidates had to meet ALL of the following criteria:

- Women age 30-39 inclusive
- Not pregnant as evidenced by one of the following:
  - Use of oral contraceptives;
  - Implanted IUD;
  - Initiation of menstruation within previous 10 days;
  - Hysterectomy;
  - Bilateral oophorectomy;
  - Tubal ligation; or
  - Negative serum HCG within previous 10 days.

EXCLUSION CRITERIA

Candidates were excluded from this study if prior to enrollment they met ANY of the following exclusion criteria:

- Pregnant;
- 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; or
- Known breast cancer.

11.2.2.2 Study Procedure

PRIOR TO TESTING

At each center, patients were offered a brief explanation of the study and technology by the principal investigator or examiner. If the patient was interested in participating, a Patient Eligibility form was completed and used to determine eligibility for the study. Each eligible patient then signed a written informed consent form that the relevant IRB (or Helsinki Committee outside the USA) approved. All required clinical data were then collected and entered on the CRF (**Appendix 11.6.2**). Informed consent was obtained from all patients who were potential study candidates prior to performance of the T-Scan™ exam.

The following baseline data were collected for all patients:

- Medical history and hormonal information, including history of previous breast surgery or biopsy;
- Clinical Breast Exam result; and
- Documented evidence of pregnancy testing or documented evidence of method to prevent pregnancy.

CLINICAL BREAST EXAMINATION

All patients had a clinical breast examination ("CBE") by a qualified examiner (typically the referring physician or the principal investigator), and the results were entered in the system database. Specific attention was paid to the clinical breast exam and the presence or absence of a palpable breast mass. Other CBE findings, including lymphadenopathy, breast pain or nipple discharge, were also documented.

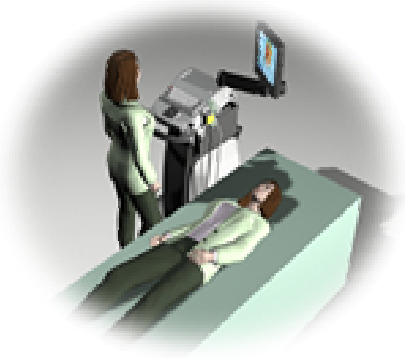

Figure 11.1 Orientation of the T-Scan device during an exam

EIS EXAMINATION

The T-Scan™ device was typically located at the head of the examination table on which the patient lay supine (Figure 11.1). The examination was performed by either the investigator or a trained designee, who entered the patient's code information, date of birth, age, CBE result, and pregnancy status.

In performing the scan, the examiner started by putting conductive gel on the metal signal transmitter and then placing the transmitter in the palm of the contralateral

hand to the breast being examined (*e.g*. the transmitter was in the left hand when examining the right breast).

The breast was then uncovered and a thin layer of conductive gel was applied to the breast and surface probe, which is the reference electrode. The surface probe was then placed on the nipple of the breast and the "START" button on the back of the surface probe was pressed. This initiated the scanning procedure by allowing the examiner to see the real-time image on the monitor display and ensure good contact prior to recording. When an adequate image was obtained, the first recording was made by depressing the "RECORD" button on the back of the probe. Once the first (nipple) sector was recorded, a graphic on the T-Scan™ display monitor indicated that the sector recording was complete and designated the location for the next sector recording. In total, nine sectors were recorded per breast following the same, predetermined pattern around the breast each time. Once the first breast was fully scanned, the T-Scan™ device prompted the examiner to begin scanning the second breast.

The examiner then asked the patient to shift the signal transmitter to her other hand and began scanning the second breast. Once the second breast was fully scanned, an audible signal alerted the examiner. The post-processing algorithm then analyzed the accumulated data in real time and displayed a "positive" or "negative" result by showing a single "green" indicator bar below the breast diagram in the case of a negative (normal) exam (Figure 11.2).

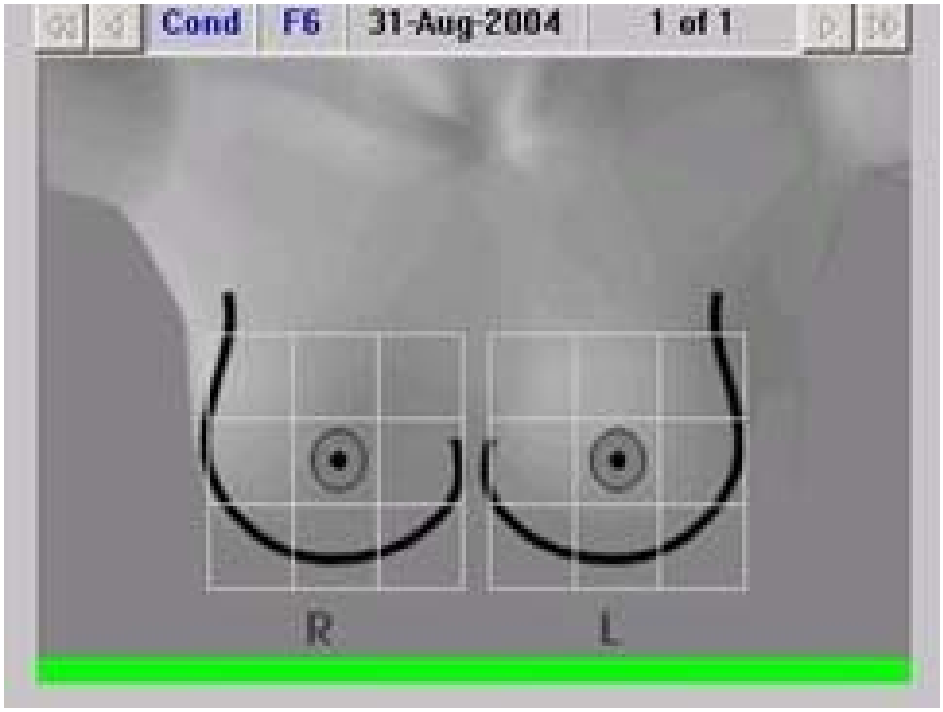

Figure 11.2 Green indicator bar, normal exam

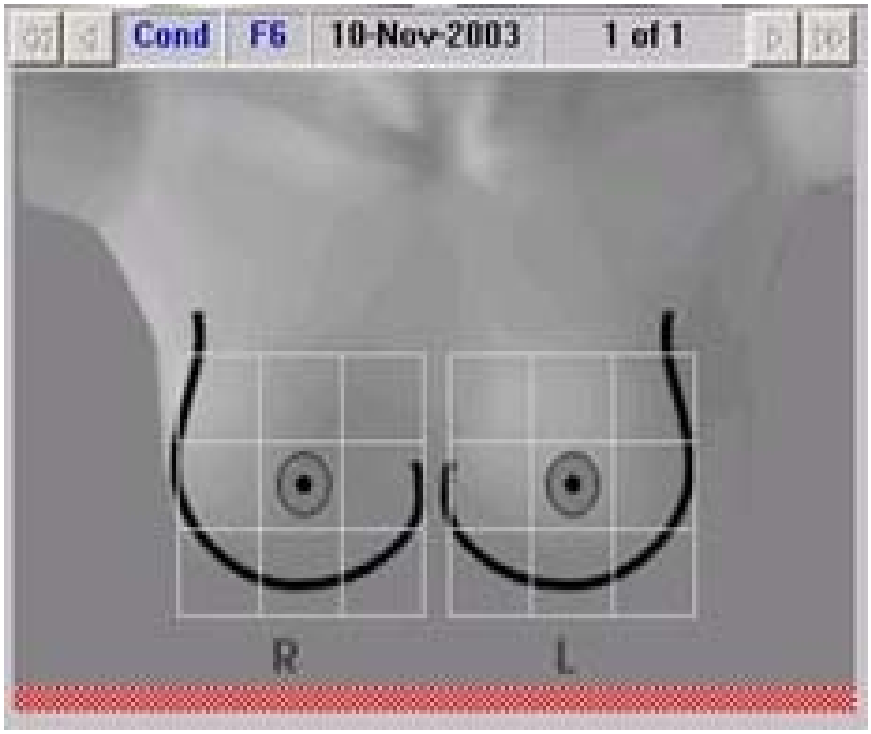

Figure 11.3 Red indicator bar, “suspicious” exam

If exam results were outside the normal range (“suspicious”), a single hatched red line was displayed (Figure 11.3).

DATA ANALYSIS

As briefly described above, the objective of the Specificity Arm of the study was to measure the specificity rate (true negative rate) in a cohort of women who are directly representative of the intended use population.

Because all women in the study (and in the target population) were young and had a negative clinical breast exam, it was assumed, for the purposes of this study, that ***all*** women in the Specificity Arm of the study were free of breast cancer. This study design is slightly biased in its assessment of specificity against the technology, because statistically, up to 4 subjects may actually have had breast cancer. In such cases, the T-Scan™ was considered falsely positive when, in fact, the device may have identified a true positive exam. This bias, however, is rather slight. Thus, for the purposes of this arm of the study, specificity was defined as the percentage of EIS negative cases.

It should be noted that the assumption that patients were free of breast cancer was not utilized in directing the patient’s clinical care. A negative T-Scan™ examination had no impact on the clinical management of the patient.

Several potential covariates were analyzed to assess their effect on specificity, including the following:

- Menopausal status (pre-versus post-menopausal)
- Exogenous hormone use
- Family history of breast cancer
- Breast size
- Race/ethnicity

Chi-square statistics were calculated to examine the relationship between specificity and each of the above covariates.

Additionally, multiple logistic regression techniques were used to examine specificity in relation to the above clinical factors with the exception of race/ethnicity, in which there was only a subset of women for whom such data was recorded.

SAMPLE SIZE JUSTIFICATION

The sample size determination for the Specificity Arm was based on having a large enough sample size so as to be able to estimate specificity with a sufficiently narrow confidence interval to obtain a clinically acceptable level of confidence.

The study design called for data to be collected until a minimum of 1,500 CBE negative patients were enrolled. Based on previous data, fewer than 10% of patients were expected to be positive on CBE. Accordingly, it was expected that approximately 1,650 women would be scanned in order to enroll the 1,500 CBE negative subjects. Previously collected data on expected specificity for the T-Scan™ device indicated that the expected specificity would be approximately 93%. Consequently, a sample size of 1,500 women would enable the study to report specificity with a 95% confidence interval within $\pm$1.3%.

SAFETY EVALUATION

All patients who had a T-Scan™ examination were queried in order to evaluate the safety of the device. Patients were asked if they felt any discomfort or pain or experienced any other adverse reactions or sensation during the examination.

There were no reported cardiac, neurological, dermal, thermal or allergic reactions or adverse events, nor any reports of patient discomfort. 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 application.

11.2.2.3 Results for Specificity Arm

CLINICAL SITES

The 17 participating clinical sites and the principal investigators at each site are listed below in Table 11.2. All participating institutions obtained IRB or Helsinki Committee approval. The sites included a mixture of academic sites and private clinical practices. The sites that participated in the pivotal study are typical of those that would use the T-Scan ED as a screening modality for young women, since all are OB/GYN clinics or breast centers with an active program of breast cancer screening. The patient population at each center consisted of routine screening patients.

Table 11.2 Clinical sites (Specificity Arm)

Abbreviation	Clinical Site	Principal Investigator(s)
[Redacted]	[Redacted]	[Redacted]

Data for this arm of the study were collected between September 1, 2003 and September 1, 2004. The number and percent of patients enrolled at each site is shown in Table 11.3 below:

Table 11.3 Enrollment by site (Specificity Arm)

Site [Redacted]	Patients		Exams Performed	
	N	%	N	%
	309	15.9%	311	15.9%
	61	3.1%	61	3.1%
	34	1.7%	34	1.7%
	48	2.5%	48	2.5%
	90	4.6%	90	4.6%
	3	0.2%	3	0.2%
	197	10.1%	197	10.1%
	165	8.5%	165	8.5%
	49	2.5%	49	2.5%
	48	2.5%	48	2.5%
	39	2.0%	40	2.1%
	280	14.4%	281	14.4%
	75	3.9%	75	3.8%
	67	3.4%	67	3.4%
	17	0.9%	17	0.9%
	87	4.5%	87	4.5%
	377	19.4%	377	19.3%
Total	**1946**	**100%**	**1950**	**100%**

PATIENT AND T-SCAN™ EXAM ACCOUNTABILITY

Data on the number of exams, patients and reasons for exclusions are presented in Table 11.4 below.

Table 11.4 Patient and T-Scan™ exam accountability (Specificity Arm)

		Number of Exams	Number of Patients
T-Scan™ exams attempted		**1,950**	**1,946**
Patient declined exam *(after being assigned a patient ID)*		2	2
Technical difficulties	*No exam results*	13	**11****
	Unreliable exam results	5	**3****
Total T-Scan™ exams with exam results		**1,935**	**1,933***
Total T-Scan™ Exams with reliable results		1930	1930
Exclusions based on eligibility criteria		179	179
Per protocol exams		**1,751**	**1,751**

**These 1933 patients constitute the analysis based on patients with available T-Scan™ exams.*

***Four patients had repeat exams (as described below). The initial exams but not the patients are excluded and the repeat exams are included in the analyses.*

A total of 1,950 T-Scan™ exams were completed or attempted on 1,946 women in the Specificity Arm. Two women (RNM 66 and PMU 152) declined the exam after being assigned a number and signing a consent form. Since no T-Scan™ exam was completed, and thus no results are available, these two women were excluded from the final data analysis.

Technical difficulties occurred during 18 examinations (0.92% of all exams). These difficulties resulted in either no exam result at all (n=13) or an unreliable exam result (n=5). The reasons for technical difficulties included:

- Mastectomy (The T-Scan™ needs information from recordings of two breasts to compute exam results) (n=2);
- Dead sensor on probe (n=7)[1];
- Repeated recording error messages during exam (n=7)[2];
- Frayed wire on signal transmitter (n=1); and
- Device locked up (n=1).

The five unreliable exam results (out of the 18 technical problems) occurred in cases where there was a frayed wire on the signal transmitter (n=1) and where repeated error messages were displayed during the exam (n=4).

The examination was repeated in 4 of the 18 patients where technical problems were encountered **[Redacted]**. In these four patients, the Examiner stopped the initial T-Scan™ exam recording and repeated the examination, assigning new case numbers to the repeated exams **[Redacted]**.

The results of the second exam, where no problems were reported, are used in the per protocol analysis for all four of the patients with repeated exams.

Finally, 179 patients did not meet all of the protocol defined eligibility criteria for the following reasons:

- Age < 30 (n=50);
- Age >39 (n=62);
- Lactating (n=3);
- Breast cosmetic surgery (n=3);
- Chemotherapy (n=2); and
- Known breast mass (*i.e.*, palpable lesion) (n=59).

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[1] When the company was notified that there was a device problem, *e.g.,* dead sensors on a probe or frayed wire on the signal transmitter, an applications specialist or service person went to the site to replace the defective part.

[2] The most common error message that interfered with recordings was "Acquisition stopped due to Overflow". If one or more sensors detects a current which is above the measurable maximum, the system tries to lower the transmission voltage. If the signal is still too high and the transmission voltage decays to below a predefined level, this message appears.

Of the 179 excluded patients due to eligibility criteria, 112 (63%) were excluded from the per protocol analysis because they were outside of the target age range. It should be noted that these violations of age related eligibility criteria occurred because this non-significant risk (NSR) study was approved with specific stipulations at certain institutions. In military hospitals, for example, the IRB and Human Use Committee were interested in evaluating the T-Scan™ device in a slightly wider age range than the protocol presented to FDA, which more accurately suited the demographics of their patient population. Thus, the protocol was modified after discussion with the sponsor to include women who are younger than 30 or older than 40 at their institution. This modification added patients to the overall database who were outside the age range; these patients are analyzed in the all patient analysis group below.

An additional 59 patients were excluded because they had palpable breast masses. As discussed with FDA, these cases were examined as part of the study, but not analyzed as part of the per protocol analysis because they are not part of the intended use population. Clinically, patients with a palpable mass must undergo radiographic follow-up with mammography, ultrasound, MRI or biopsy irrespective of T-Scan™ results. As a result, women with palpable masses would not benefit from being screened with the T-Scan™ device.

Thus, 171 of the 179 excluded patients for whom exam results are available (96%) are accounted for by either the “age out of range” or “palpable mass” exclusion criteria. An analysis of the entire examined population, as well as the narrower per protocol cohort, is included in this submission.

In summary, T-Scan™ examination data were attempted on 1,950 exams in 1,946 patients of which 199 exams and 195 patients are excluded from the per protocol analysis resulting in a total of 1751 exams and 1751 patients for the per protocol analysis.

BASELINE CHARACTERISTICS OF CASES IN SPECIFICITY ARM

Baseline characteristics for cases in the Specificity Arm are presented in Table 11.5.

Table 11.5 Baseline characteristics of per protocol cases (Specificity Arm)

Baseline Characteristics	N	%
Menopausal Status		
Pre-Menopausal	1718	98.1%
Post-Menopausal	32	1.8%
Missing	1	0.1%
Hormone Usage		
No hormone use	968	55.3%
Estrogen compounds	588	33.6%
Progesterone only compounds	96	5.5%
Other	15	0.9%
Missing	84	4.8%
Brassiere Cup Size		
A or B	839	47.9%
C or D	794	45.3%
More than D	84	4.8%
Missing	34	1.9%
Number of 1st degree relatives with breast cancer		
0	1558	89.0%
1 or more	163	9.3%
Missing	30	1.7%
Race/Ethnicity		
Asian	26	1.5%
American Indian	9	0.5%
Black	51	2.9%
Hispanic	48	2.7%
Caucasian	865	49.4%
Missing	752	42.9%
Age		
Mean (Std.)	1751	34.7 (2.8)
Range	1751	30 – 39

OVERALL SPECIFICITY

Specificity for all available cases and per protocol cases is shown in Table 11.6 below.

Table 11.6 Overall specificity (Specificity Arm)

Patient Population	N	T-Scan™ Negative	Specificity
Per protocol	1751	1658	94.7%
All data available*	1933	1827	94.5%

**All data available includes all patients with a valid T-Scan™ result*

Of the excluded cases, perhaps the most important subgroup is that of women with an abnormal CBE (palpable mass). Specificity for women with normal and those with abnormal CBE is shown in Table 11.7 below.

Table 11.7. Specificity by CBE result (Specificity Arm)

	N	T-Scan™ negative	Specificity	p-value
Normal CBE	1751	1658	94.7%	0.94
Abnormal CBE	59	56	94.9%	

While this subgroup is not clinically relevant to the target population since women with a palpable mass are not indicated for a T-Scan™, it is, nevertheless, relevant to the interpretation of data in the Sensitivity Arm of this study (see below) where a large proportion of women had palpable lesions.

Data presented in the tables above (Tables 11.6 and 11.7) strongly suggest that the inclusion of all cases (including those excluded for technical problems) has a negligible impact on the overall estimates of device specificity (94.7% vs. 94.5%). For this reason, the remainder of this analysis is devoted to the per protocol cases so as to adequately reflect results in the intended use population.

Because specificity patients were not followed up, there is a possibility that a very small number of patients, *e.g.*, up to 4, were ultimately determined to have cancer and thus, the assumption that all positive exams in this arm of the study are false positives may not necessarily be correct. However, as mentioned earlier, this possibility would serve to improve the final specificity result. Because the impact of this possibility would be rather small (less than 1%) and because it slightly biases the result against the technology, it was deemed acceptable to accept this bias as opposed to mandate a specific regimen of follow-up based upon the result of an experimental device.

The overall specificity in the per-protocol population was 94.7% (1658/1751) with a 95% confidence interval of (93.7%, 95.7%).

SPECIFICITY ANALYZED BY SITE

Specificity broken down by participating clinical site is shown in Table 11.8.

Table 11.8 Specificity by participating site (Specificity Arm)

Site [Redacted]	N	T-Scan™ Negative	Specificity
	303	295	97.4%
	59	57	96.6%
	33	32	97.0%
	47	47	100.0%
	88	85	96.6%
	2	2	100.0%
	149	133	89.3%
	163	146	89.3%
	29	27	93.1%
	47	45	95.7%
	35	31	88.6%
	267	260	97.4%
	74	71	97.3%
	66	63	95.5%
	17	14	84.4%
	28	26	92.9%
	344	324	94.2%
Total	1751	1658	94.7%

As summarized in the table above, sites differed in specificity around the mean specificity of 94.9% (Likelihood Ratios $\chi 2=36.62$, $p<0.005$).

Of 17 sites included in the Specificity Arm, one site **[Redacted]** had a significantly lower specificity than all other sites (84.4 % at **[Redacted]**, compared to the average across all 16 other sites of 94.8%). While this site contributed 1% of cases in the Specificity Arm (17 cases vs. average recruitment of 108.3 cases/site across the remaining 16 sites), it was responsible for almost 14% of the chi-square value for variability between sites. The specificity may have been lower in this site due to a low recruitment rate and multiple examiners resulting in relative inexperience conducting the T-Scan™ exam. Importantly, estimates of specificity from all other sites were closely grouped, ranging from 89% to 100%.

ANALYSIS OF COVARIATES FOR SPECIFICITY

Race/ethnicity was recorded only when the examiner filled out the Gail Scale[1] report in the Patient Data screen. However, Gail Scale (Gail *et al*., 1989) information was not a required part of this study, and hence the report was not completed for any patient outside the U.S. Race/ethnicity was recorded for 999 of the 1,285 patients from the United States. Most women outside the U.S. were Caucasians. Pearson's chi-square was used to examine the

relationship between specificity and racial/ethnic classification for the subset of cases recorded in the United States (Table 11.9).

Table 11.9 Specificity by racial and ethnic groups (Specificity Arm)

Race/Ethnicity	N	T-Scan™ Negative	Specificity
Caucasian	865	827	95.6%
Black	51	45	88.2%
Hispanic	48	42	87.5%
Asian	26	26	100%
American Indian	9	9	100%
Missing	752	709	94.3%

The racial/ethnic groups did differ significantly in specificity (Pearson $\chi 2=12.8$, $p<0.05$). The relationship between specificity and ethnicity is discussed more fully in Amendment 1 to this PMA.

Table 11.10. Specificity by covariates (Specificity Arm)

Baseline Characteristics	N	T-Scan™ Negative	Specificity
Menopausal Status			
Pre-Menopausal	1718	1626	94.6%
Post-Menopausal	32	31	96.9%
Missing	1	1	100.0%
Hormone Usage			
No hormone use	968	918	94.8%
Estrogen compounds	588	559	95.1%
Progesterone only compounds	96	88	91.7%
Other	15	14	93.3%
Missing	84	79	94.0%
Bra Size			
A or B	839	812	96.8%
C or D	794	740	93.2%
More than D	84	76	90.5%
Missing	34	30	88.2%
Number of 1st Degree Relatives with Cancer			
None	1558	1469	94.3%
One or more	163	159	97.6%
Missing	30	30	100.0%

Pearson's chi-square was also used to examine the relationship between specificity and brassiere cup size, menopausal status, hormone use and family history. Specificity in each of these groups is shown in Table 11.10. There was no significant ($p>0.05$) correlation between EIS results and family history, menopausal status, and use of exogenous hormones.

Brassiere cup size was associated (Pearson $\chi 2=16.6$ $p=0.001$) with positive EIS findings; namely, the rate of FP exams increased with increasing cup size. However, it should be noted that even in the largest cup sizes (which represented <5% of patients), specificity was almost 91%. This may be explained by the fact that electrical impedance measurements are correlated with both body fat and skin thickness, and further, body fat and skin thickness are correlated with each other (Hansen *et al.*, 1997). In addition to the direct effects on electrical impedance measurements, it can be harder to obtain contact between the surface probe and skin in large breasted women because it is harder to flatten out the breast.

Logistic regression analysis was also used to examine the covariates of brassiere cup size, menopausal status, hormone use and family history on specificity. Again, bra size was the only significant covariate with a p-value of <0.001.

CONCLUSION FOR THE SPECIFICITY ARM

The overall specificity for per protocol cases in the Specificity Arm was 94.7%. This specificity was unaffected by presence of a palpable mass, menopausal status, hormone use, family history of breast cancer or racial/ethnic group. It was significantly related to brassiere cup size, being lower (although still above 90%) for larger breasted women.

11.2.3 Sensitivity (Biopsy) Arm

11.2.3.1 Summary of Protocol

Below is a summary of the protocol for the Sensitivity Arm of the two-arm study. The entire protocol is attached to the complete PMA application as **Appendix 11.6.1.**

It should be noted that all patients in the Specificity Arm (above) were in the intended use population of women age 30-39. The Sensitivity Arm, however, was cancer-enriched by enrolling patients who were scheduled for biopsy based on prior clinical findings, including palpability, in an expanded age range of patients from 30-45 (as opposed to 30-39 in the Specificity Arm). FDA accepted this study population (June 2, 2003) in order to allow more expeditious accrual of cancer patients, while maintaining breast tissue features that are generally consistent with the intended use population.

This decision was further supported by previous experience with EIS measurements (Piperno and Lenington, 2002), which indicate that the principal factor affecting breast electrical recording characteristics is the hormonal changes occurring at menopause and not age *per se* (Piperno and Lenington, 2002). FDA agreed that the initiation of mammography at age 40 is not associated with any particular breast tissue differences, and that tissue changes are associated with menopausal status more than age. Thus, it was agreed that including patients up to age 45 was acceptable as long as any menopausal patients are excluded, and that separate analyses were included for sensitivity in women age 30-39 and women 40-45.

Physicians were blinded to the T-Scan™ result, and, of course, to the biopsy report which followed. Sensitivity was then estimated by comparing T-Scan™ results against biopsy results for the 87 women who were found to have biopsy confirmed breast cancer.

All patients who met the inclusion criteria and who were willing to take part in the study were introduced to the technology, consented and examined (scanned) with the T-Scan ED device. This arm of the study involved testing women prior to their biopsy procedure.

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

For purposes of this study:

- A TP case was defined as one that was positive on T-Scan and positive on pathology.
- A FN case was defined as one that was negative on T-Scan and positive on pathology.
- A TN case was defined as one that was negative on T-Scan and negative on pathology.
- A FP case was defined as one that was positive on T-Scan ED and negative on pathology.

Women were considered positive for breast cancer only if they had histological confirmation of malignancy.

The effect of the same covariates that were examined in the Specificity Arm of the study (with the exception of race/ethnicity) also was examined on sensitivity for cancers and specificity for benign lesions. In addition, the relationship between sensitivity and size of cancer was analyzed.

Lesion size was determined on the basis of biopsy size, if available. If biopsy size data were not available, lesion size was based on ultrasound or mammography in that order (except for cancers present solely on mammography as microcalcifications, for which no size data were available). Finally, when no size data were available from any imaging modality, size was estimated by the recorded size based on palpation.

Mammographic and ultrasound findings were entered from the radiology reports and entered on the CRF after the T-Scan™ examination was completed. Biopsy findings would typically be obtained some days later for inclusion in the CRF, as were pathology findings for biopsy patients. As data were obtained for each patient, they were entered on the CRF.

CLINICAL SITES

This Sensitivity Arm of the study was carried out at 18 clinical sites. The sites included both academic institutions and private surgery/radiology practices. Study sites were selected because each had the following characteristics useful for the present study:

- an active breast biopsy practice including young women patients;
- an expressed interest in new diagnostic modalities; and
- previous participation in clinical research such that the investigators were familiar with the required procedures and concepts.

The personnel designated at each site (PI, Data Coordinator, Examiner) and their duties were the same as in the Specificity Arm with the exception that the Data Coordinator was also required to provide results of imaging (ultrasound/mammography) exams and pathology reports when available.

PATIENT ENROLLMENT

All patients scheduled for breast biopsy were eligible for enrollment in the study. These women were evaluated against the study inclusion and exclusion criteria outlined in this protocol. Enrollment in the study occurred at the time the study informed consent was obtained.

INCLUSION CRITERIA

Prior to enrollment in the Sensitivity Arm of the study, candidates had to meet ALL of the following inclusion criteria:

- Women ages 30-45 inclusive;
- Scheduled for breast biopsy; and
- Not pregnant as evidenced by one of the following:

- Use of oral contraceptives;
- Implanted IUD;
- Initiation of menstruation within previous 10 days;
- Hysterectomy;
- Bilateral oophorectomy;
- Tubal ligation; or
- Negative serum or urine HCG within previous 10 days.

EXCLUSION CRITERIA

Candidates were excluded from the study if prior to enrollment if they met ANY of the following exclusion criteria:

- Pregnant;
- Previous breast cosmetic surgery;
- Breast fine needle aspiration (FNA) within the previous 1 month;
- Core/excisional biopsy within the previous 3 months;
- Breast-feeding within the previous three months;
- Presence of an electrically powered implanted device, *e.g.,* pacemaker;
- History of or currently undergoing chemotherapy

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 of the study except that women with a palpable mass were excluded in the Specificity Arm but included in the Sensitivity Arm.

STUDY PROCEDURE

Prior to Testing

At each center, patients of the appropriate age scheduled for routine examination were given a brief explanation of the study by the principal investigator. If the patient was interested in the study, a Patient Eligibility form was completed in which the eligibility of the patient for the study was documented. Each eligible woman then signed a written consent form that had been approved by the IRB (or Helsinki Committee outside the USA) of the center and clinical data were collected and entered on the CRF form. Informed consent was obtained from all patients who were potential study candidates prior to performance of the diagnostic test.

The following baseline data were collected for all patients:

- Medical history including previous breast surgery or biopsy and hormonal information);
- Clinical Breast Exam result; and
- Documented evidence of pregnancy testing or documented evidence of methods to prevent pregnancy.

The CBE was identical to that described in the Specificity Arm of this study.

The EIS Examination

The T-Scan ED examinations performed in the Sensitivity and the Specificity Arms (see above) were identical except that examiners in the Sensitivity sites were "blinded" as to the results of the T-Scan ED examination such that neither a green nor a red line appeared next to the image of the patient's breasts at the end of the examination.

Upon completion of the T-Scan ED examination, the patients had a biopsy performed as scheduled. The results of the biopsy provided the confirmatory diagnosis for the patient. In some cases, T-Scan™ was performed, but the patient did not have a biopsy because further evaluation by the physician determined that a biopsy was not clinically warranted (for example, ultrasound evaluation showed the mass to be a simple cyst).

BIOPSY RESULTS

Histological diagnosis was performed by experienced breast pathologists. A requirement of the study was that the diagnosis be clear, simple and unambiguous. For example, for benign diagnoses, it was necessary to indicate whether the lesion was a fibrocystic change or a proliferative disorder such as fibroadenoma, hyperplasia or atypical hyperplasia - a blanket diagnosis of "fibrocystic disease" was unacceptable. To this end, a minimal list of diagnostic terms was agreed upon by the study participants and included in the CRF.

For the purposes of this study, atypical hyperplasia and lobular carcinoma in situ ("LCIS") were regarded as a benign finding, not a malignant lesion.

DATA ANALYSIS

The objective of the Sensitivity Arm of the study was to measure the device sensitivity (true positive rate) for the detection of breast cancer. The secondary objective was specificity for benign lesions. These data were to be analyzed on pre-menopausal women.

In addition, several covariates were analyzed to assess their effect on sensitivity for cancers and specificity for benign lesions. These covariates were:

- Exogenous hormone use;
- Family history of breast cancer;
- Breast size;
- Presence or absence of a palpable lesion; and
- Size of lesion (cancers only).

SAMPLE SIZE JUSTIFICATION

As discussed below, the final outcome measure for this study is relative probability (the probability that a T-Scan™ positive woman has cancer relative to that for a randomly selected woman from the population at large). Relative probability is calculated using the estimates of sensitivity (from the Sensitivity Arm) and specificity (from the Specificity Arm) as well as the prevalence of cancer in the population. In the Sensitivity Arm of the study the sample size of 100 cancers was proposed in order to obtain an estimate of sensitivity with reasonable confidence intervals that could be used to calculate relative probability.

Women under the age of 40 are, as per standard of care, often sent for mammographic or ultrasound breast cancer screening if they have family history or other risk factors that double their risk of having breast cancer (Duffy *et al.*, 1997) *i.e.*, if they have a relative risk $\geq$2.

It was assumed at the start of the study that the sensitivity of the T-Scan™ for cancer would be between 20-30% and therefore that it would be necessary to obtain data on 100 cancers to obtain a risk multiple of 2 with adequate confidence intervals. In fact, both sensitivity and specificity of the T-Scan ED have been higher than expected at the start of the study. After extensive discussions with the Agency, it was determined that the lower confidence bound of relative probability would be greater than 2 even if no further cancers were detected with the T-Scan ED over of the next series of 30 biopsy proven cancers. Hence, the FDA agreed to allow the Company to submit the original PMA application with 68 rather than 100 cancers. Since the original submission in December, 2004, the Company has collected data on 19 more cancers. Hence, the sensitivity results in this Amendment are based on 87 per protocol cancers.

SAFETY EVALUATION

All patients who had a T-Scan™ examination were queried in order to evaluate the safety of the device. Patients were asked if they felt any discomfort or pain or experienced any other adverse reaction or sensation during the examination.

There were no reported cardiac, neurological, dermal, thermal or allergic reactions or adverse events, or any reports of patient discomfort. 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 application.

11.2.3.2 Results for Sensitivity Arm

CLINICAL SITES

The sites that enrolled patients in the Sensitivity Arm of the study are listed in Table 11.11 below.

Table 11.11 Clinical sites (Sensitivity Arm)

Abbreviation	Clinical Site	Principal Investigator(s)
[Redacted]	[Redacted]	[Redacted]

Data for this arm of the study were collected between August 7, 2003 and July 14, 2005. The number and percent of patients enrolled at each site are shown in Table 11.12.

11.12 Enrollment by site (Sensitivity Arm)

Site [Redacted]	Total	
	N	%
	31	5.2%
	33	5.5%
	18	3.0%
	120	20.1%
	31	5.2%
	18	3.0%
	55	9.2%
	13	2.2%
	49	8.2%
	1	0.2%
	26	4.3%
	6	1.0%
	8	1.3%
	37	6.2%
	37	6.2%
	56	9.4%
	38	6.4%
	21	3.5%
Total	598	100.0%

PATIENT AND T-SCAN™ EXAM ACCOUNTABILITY

Data on the number of exams, patients and reasons for exclusions are presented in Table 11.13 below.

Table 11.13 Patient and T-Scan™ exam accountability (Sensitivity Arm)

	Total Exams	Total Patients
T-Scan™ exams attempted	598	597
Patient declined exam *(after being assigned a patient ID)*	4	4
Technical difficulties - no T-Scan™ results available	4	4
No Biopsy Results	44	44
Repeated exam	1	-
T-Scan™ exams with results*	545	545

Technical difficulties - T-Scan™ results available	66	66
Exclusions based on eligibility criteria	89	89
Per protocol exams	390	390

**These exams (131 malignant, 414 benign) constitute the all data available analyses.*

Of the total 598 patients in the Sensitivity Arm, 70 cases were excluded because of problems with the exam that resulted in unreliable, incomplete, or no exam results. The reasons cases were excluded for technical reasons included:

- Mechanical Probe Failure (64);
- Dead sensor on probe (4)[3]; and
- Repeated recording error messages during exam (2)[4].

No exam results were available for the cases with a dead sensor on the probe. Exam results (albeit unreliable) were available for two cases with repeated recording error messages (in the 2nd case, the exam was stopped in the middle, so no results were available) and the 64 cases with manufacturing problems in the probe; these 66 cases are included in the all data available analysis but excluded from the per protocol analysis.

Finally, 133 cases did not meet all of the protocol defined eligibility criteria:

- No biopsy result (n=44);
- Age < 30 (n=26);
- Age >45 (n=28);
- Chemotherapy (n=8);
- Lactating (n=2);
- Biopsy within the preceding 90 days (n=1);
- Post-menopausal (n=24)[5]; and

[3] When the company was notified that there was a device problem, *e.g.* dead sensors on a probe or frayed wire on the signal transmitter, an applications specialist or service person went to the site to replace the defective part

[4] The most common error message that interfered with recordings was "Acquisition stopped due to Overflow". If one or more sensors detect a current which is above the measurable maximum, the system tries to lower the transmission voltage. If the signal is still too high and the transmission voltage decays to below a predefined level, the error message appears.

[5] In the protocol it was stated that the analysis of sensitivity would be restricted to pre-menopausal women (even through they were not specifically excluded in the eligibility criteria). The reason for so restricting the analysis was to ensure that the population of women over the age of 39 included in this Arm of the study still manifested the same hormonal/physiological conditions as women in the Specificity Arm.

Of these 133 cases, 44 did not have a biopsy result. Biopsy results were missing for the following reasons:

- After the patient was enrolled, it was decided on the basis of other imaging exams that a biopsy was not needed (n=34);
- The patient canceled the scheduled biopsy or declined to have a biopsy (n=4);
- The biopsy was done at another institution and the result was not available (n=2);
- A biopsy was done but the histological diagnosis that was available at the close of the study did not unambiguously determine whether the woman had cancer (n=2); and
- The reason for not having a biopsy result was not documented (n=2).

As in the Specificity Arm, some of these eligibility violations occurred because these patients were scanned at institutions where the inclusion criteria in the IRB approved protocol were somewhat broader than they were for the FDA study. In addition, at several sites, patients were enrolled because they had abnormal mammograms or other exams and the investigator thought the patient might be a likely candidate for biopsy. However, after further imaging, it was decided no biopsy was needed. Such women are excluded from the per protocol analyses in this arm of the study.

The per protocol population (N=390) is the population on which the main analyses will be based. However, the overall sensitivity and specificity results are reported for both the per protocol population and the all data available population (N=545).

The per protocol contribution of each site to the Sensitivity Arm is shown in Table 11.14 below.

Table 11.14 Number of per protocol patients by type of lesion and study site (Sensitivity Arm)

Site [Redacted]	Malignant		Benign		Total	
	N	%	N	%	N	%
	10	11.49%	15	4.95%	25	6.41%
	6	6.90%	19	6.27%	25	6.41%
	1	1.15%	13	4.29%	14	3.59%
	16	18.39%	66	21.78%	82	21.03%
	4	4.60%	13	4.29%	17	4.36%
	2	2.30%	10	3.30%	12	3.08%
	8	9.20%	32	10.56%	40	10.26%
	4	4.60%	5	1.65%	9	2.31%
	8	9.20%	34	11.22%	42	10.77%
	0	0.00%	1	0.33%	1	0.26%
	4	4.60%	21	6.93%	25	6.41%
	1	1.15%	3	0.99%	4	1.03%
	2	2.30%	6	1.98%	8	2.05%
	15	17.24%	14	4.62%	29	7.44%
	3	3.45%	14	4.62%	17	4.36%
	0	0.00%	25	8.25%	25	6.41%

Site [Redacted]	Malignant		Benign		Total	
	N	%	N	%	N	%
	3	3.45%	12	3.96%	15	3.85%
Total	87	100.00%	303	100.00%	390	100.00%

BASELINE CHARACTERISTICS OF CASES IN THE SENSITIVITY ARM

Of the 390 per protocol cases in the Sensitivity Arm, 87 had cancer and 303 had benign lesions. The mean age of cancer cases was 39.5 (SD= 3.9, range 30-45). Mean age for benign cases was 38.8 (SD=4.3, range 30-45). Baseline characteristics for each group are presented in Table 11.15 below.

Table 11.15 Baseline characteristics of per protocol cases (Sensitivity Arm)

Baseline Characteristic	Cancer Cases (N=87)		Benign Cases (N=303)		Total Cases (N=390)	
	N	%	N	%	N	%
Age						
30-39	37	42.53%	142	46.86%	179	45.90%
40-45	50	57.47%	161	53.14%	211	54.10%
Mean (Std)	87	39.5 (3.9)	303	38.8 (4.3)	390	38.9 (4.2)
Range	87	30 - 45	303	30 - 45	390	30 - 45
CBE						
Normal CBE	17	19.54%	131	43.23%	148	37.9%
Abnormal CBE	70	80.46%	172	56.77%	242	62.1%
Hormone Usage						
No hormone use	57	65.5%	227	74.9%	284	72.8%
Compounds with estrogen (with or without progesterone)	7	8.0%	21	6.9%	28	7.2%
Compounds with only progesterone	2	2.3%	6	2.0%	8	2.1%
Other	1	1.1%	6	2.0%	7	1.8%
Missing	20	23.0%	43	14.2%	63	16.2%
Bra Cup Size						
A and B	26	29.9%	121	39.9%	147	37.7%
C and D	34	39.0%	133	43.9%	167	42.8%
>D	3	3.4%	23	7.6%	26	6.7%
Missing	24	27.6%	26	8.6%	50	12.8%

Baseline Characteristic	Cancer Cases (N=87)		Benign Cases (N=303)		Total Cases (N=390)	
	N	%	N	%	N	%
Number of First Degree Relatives with Breast Cancer						
None	68	78.2%	248	81.8%	316	81.0%
One or more	13	14.9%	52	17.2%	65	16.7%
Missing	6	6.9%	3	1.0%	9	2.3%
Size of Lesion (mm)						
≤ 20	45	51.7%	165	54.5%	210	53.8%
> 20	27	31.0%	39	12.9%	66	16.9%
Missing	15	17.2%	99	32.7%	114	29.2%
Mean (Std)	72	22.9 (15.1)	204	15.8 (9.8)	276	17.6 (11.8)
Range	72	5-80	204	3-78	276	3-80

The biopsy diagnosis for cancer cases is presented in Table 11.16 below.

Table 11.16 Biopsy diagnosis for cancer cases (Sensitivity Arm)

Malignant Diagnosis	N	%
Ductal carcinoma in situ	14	16.1%
Invasive ductal carcinoma	47	54.0%
Invasive ductal carcinoma and ductal carcinoma in situ	22	25.3%
Invasive lobular carcinoma	1	1.2%
Invasive lobular carcinoma and invasive ductal carcinoma	2	2.4%
Invasive lobular carcinoma and ductal carcinoma in situ	1	1.2%
Total	87	100%

The breakdown of benign cases by diagnosis is shown in Table 11.17 below.

Table 11.17 Biopsy diagnosis for benign cases (Sensitivity Arm)

Diagnosis	N	%
Fibroadenoma	72	23.76%
Fibrosis	37	12.21%
FCC	35	11.55%
Hyperplasia	29	9.57%
Sclerosing Adenosis	26	8.58%
Cyst	26	8.58%
Adenosis	21	6.93%
Normal	13	4.29%
Atypia	8	2.64%
Papilloma	6	1.98%
Lipoma	6	1.98%
Inflammation	6	1.98%
Phyllodes Tumor	4	1.32%
Lobular Hyperplasia	3	0.99%
Papillomatosis	2	0.66%
Lymph Node	2	0.66%
Tubular Adenoma	1	0.33%
Radial Scar	1	0.33%
Lactating Features	1	0.33%
Fibroadenosis	1	0.33%
Fat Necrosis	1	0.33%
Fat	1	0.33%
Benign	1	0.33%
Total	303	100%

SENSITIVITY

Of the 390 per protocol cases in the Sensitivity Arm, 87 (22.3%) were found to have cancer. Sensitivity for cancers for per protocol and all cases are presented in Table 11.18 below.

Table 11.18 Overall sensitivity (Sensitivity Arm)

Patient Population	N	T-Scan™ Positive	Sensitivity
Per protocol	87	23	26.4%
All data available	131	30	22.9%

As can be seen from Table 11.18, the difference in sensitivity between per protocol cases and all available cases is small. Hence, the following analysis will be based on the per protocol cases.

SENSITIVITY BY CLINICAL SITE

Sensitivity results for each site are presented in Table 11.19. No significant difference in sensitivity was found among the investigational sites (Pearson's $\chi 2=14.0$, $p>0.10$).

Table 11.19 Sensitivity by participating site (Sensitivity Arm)

	Cancerous Lesions (N=87)		
Site [Redacted]	**Biopsy Positive Lesions**	**T-Scan™ Positive**	**Sensitivity**
	10	1	10.0%
	6	0	0.0%
	1	0	0.0%
	16	5	31.3%
	4	2	50.0%
	2	0	0.0%
	8	3	37.5%
	4	1	25%
	8	2	25%
	4	0	0.0%
	1	0	0.0%
	2	1	50.0%
	15	8	53.3%
	3	0	0.0%
	3	0	0.0%
Total	87	23	26.4%

ANALYSIS OF COVARIATES FOR SENSITIVITY

Sensitivity as a function of several covariates (patient age, brassiere cup size, hormone use, family history, palpability and lesion size of cancer) is shown in Table 11.20 below. Information concerning lesion size was available for 72 of the 87 cancers. Of the remaining 15 cancers, eight were detected as microcalcifications on mammography. These eight did not have a measurable finding on ultrasound, and size was not specifically provided in the pathology report. Size was not provided on either the imaging or pathology reports for the remaining seven cancer cases.

Table 11.20 Sensitivity by covariates (Sensitivity Arm)

Baseline Characteristics	N	T-Scan™ Positive	Sensitivity
Age			
30-39	37	7	18.9%
40-45	50	16	32.0%
CBE			
Normal CBE	17	5	29.4%
Abnormal CBE	70	18	25.7%
Lesion Size			
≤ 20mm	45	16	35.6%
> 20mm	27	6	22.2%
Missing	15	1	6.7%
Brassiere Cup Size			
A and B	26	4	15.4%
C and D	34	8	23.5%
>D	3	2	66.7%
Missing	24	9	37.5%
Hormone Usage			
No hormone use	57	12	21.1%
Compounds with estrogen (with or without progesterone)	7	2	28.6%
Compounds with only progesterone	2	1	50.0%
Other	1	0	0.0%
Missing	20	8	40.0%
Number of First Degree Relatives with Breast Cancer			
None	68	17	25.0%
One or more	13	4	30.8%
Missing	6	2	33.3%

Pearson's chi-square was used to examine the relationship between sensitivity and each of the above covariates (Table 11.20). There was no significant ($p > 0.10$) correlation between EIS results and the above categorizations of patient age, brassiere cup size, hormone use, family history of cancer, palpability of lesion, and cancer (lesion) size.

However, sensitivity data, although not statistically significant, show a similar trend of a higher sensitivity for smaller cancers (Kolb *et al.*, 2002; Fuchsjaeger *et al*., 2002; Wersebe *et al*., 2002) also seen in other EIS studies. Namely, sensitivity appears to be highest for smaller carcinomas (≤20mm) as opposed to larger ones (>20mm) (*i.e.*, 35.6% *vs*. 22.2% respectively).

SPECIFICITY FOR BENIGN LESIONS

Of the 390 per protocol cases in the Sensitivity Arm of the study, 303 (77.7%) had pathology confirmed benign lesions. Specificity for per protocol cases and all available cases is shown in Table 11.21 below.

Table 11.21 Overall specificity (Sensitivity Arm)

Patient Population	N	T-Scan™ Negative	Specificity
Per protocol	303	245	80.9%
All data available	414	339	81.9%

As can be seen from this table, the difference in specificity between per protocol and all available cases was very small. Hence, the remainder of this analysis will be based on per protocol cases.

Fifty-eight of these 303 women (19.1%) had positive EIS examinations, yielding a specificity for women with benign breast pathology of 80.9% (245/303) with a 95% confidence interval of (76.5%, 85.0%).

The specificity of 80.9% was significantly lower than the specificity of 94.7% found in the Specificity Arm of the study (Pearson's $\chi 2=72.54$, $p<0.001$). Although women with symptomatic breast pathology are not part of the intended use population, specificity was examined in the Sensitivity Arm of the study in order to validate the non-random aspect of the technology. It has been reported that women who have a breast biopsy, regardless of their diagnosis, are approximately 2 to 5 times as likely as women from the general population to ultimately develop breast cancer (Hutchinson *et al*., 1980, Potter *et al.,* 1968, Krieger and Hyatt, 1992).

It has been hypothesized (Dickhaut, 1996; Cuzick *et al.*, 1998) that electrical measurements identify pathological changes in breast tissue that precede the development of carcinoma. Consistent with this hypothesis, the rate of positive T-Scan™ exams among women with benign lesions in the Sensitivity Arm was higher than that among normal, asymptomatic women. The false positive rates were 19.1% and 5.3%, respectively.

Specificity for benign lesions at the various clinical sites is shown in Table 11.22 below. No significant difference in specificity for benign lesions was found among the participating clinical sites (Pearson's $\chi 2=18.3$, $p>0.10$).

Table 11.22 Specificity by participating site (Sensitivity Arm)

Site [Redacted]	Benign Lesions (N=303)		
	Biopsy Negative	T-Scan™ Negative	Specificity
	15	14	93.3%
	19	17	89.5%
	13	10	76.9%
	66	50	75.8%
	13	6	46.2%
	10	8	80.0%
	32	24	75.0%
	5	4	80.0%
	34	30	88.2%
	1	1	100.0%
	21	19	90.5%
	3	3	100.0%
	6	5	83.3%
	14	11	78.6%
	14	14	100.0%
	25	19	76.0%
	12	10	83.3%
Total	303	245	80.9%

Table 11.23 shows the percentage of EIS positive benign biopsy cases for the covariates measured in this study.

Table 11.23 Specificity by covariates (Sensitivity Arm)

	Benign Lesions (N=303)			
Baseline Characteristic	**N**	**T-Scan™ Negative**	**Specificity**	**p-value**
Age				
30 – 39	142	123	86.6%	0.02
40 – 45	161	122	75.8%	
CBE Result				
Normal CBE	131	104	79.4%	0.57
Abnormal CBE	172	141	82.0%	
Brassiere Cup Size				
A and B	121	108	89.3%	<0.01
C and D	133	103	77.4%	
>D	23	14	60.9%	
Missing	26	20	76.9%	

	Benign Lesions (N=303)			
Baseline Characteristic	**N**	**T-Scan™ Negative**	**Specificity**	**p-value**
Hormone Use				
No hormone use	227	185	81.5%	>0.1
Compounds with estrogen (with or without progesterone)	21	19	90.5%	
Compounds with only progesterone	6	4	66.7%	
Other	6	5	83.3%	
Missing	43	32	74.4%	
Number of 1st degree relatives with breast cancer				
None	248	202	81.5%	0.45
One or more	52	40	76.9%	
Missing	3	3	100.0%	
Lesion Size				
≤ 20mm	165	128	77.5%	0.17
20mm	39	34	87.2%	
Missing	99	83	83.8	

Pearson's chi-square was used to examine the relationship between specificity in women with benign lesions and each of the above covariates independently (Table 11.23). No significant ($p>0.10$) correlation was found between EIS results and hormone use, family history of breast cancer, palpability, or lesion size. T-Scan™ exam results were, however, found to be significantly associated with breast size ($p<0.01$), indicating lower specificity for larger as opposed to smaller bra cup size (Specificity 89.3% cup size A or B, 77.4% cup size C or D, 60.9% cup size >D). It should be noted that cup size D or greater is relatively uncommon and represented only 7.6% of this cohort. Age was also found to be an independent factor affecting specificity ($p<0.05$), with greater specificity in younger women than in older (specificity 86.6 % in women 30-39, and 75.8% in women 40-45). When used in a multiple logistic regression, bra size showed a significant independent effect ($p=0.001$) on specificity, whereas age did not ($p=0.16$).

Other covariates were excluded from the model because they were not significantly associated with T-Scan™ result.

CONCLUSION FROM SENSITIVITY ARM

The overall sensitivity for cancers was 26.4%. Sensitivity was unrelated to the covariates of age, palpability, family history, bra size or hormone use. Specificity for benign lesions was

80.9%. Specificity for benign lesions was also not related to the covariates of palpability, family history, or hormone use. However, specificity for benign lesions was related to bra size and age category and was better for younger women and those with smaller bra cup sizes. Sensitivity showed a statistically non-significant relationship with cancer size being higher for smaller cancers. Although this difference was not statistically significant, it was consistent with the trend found in other EIS studies of higher sensitivity for EIS technology for small cancers.

11.2.4 Final Outcome Measure: Combining Results of the Two Arms of the Study

11.2.4.1 Evaluation of Primary Endpoint

The anticipated clinical efficacy of the T-Scan ED device in 30-39 year old, asymptomatic women is related to the T-Scan ED's ability to detect differences in electrical impedance that are associated with an increased risk of breast cancer. In order to accurately measure device performance in this particular context, and contrast these results with the accepted standard of care, two principal decisions were made with input from both the clinical community and the FDA:

- How to measure device performance in identifying increased risk for breast cancer in the target population; and
- The standard of care for breast cancer risk identification and the accepted recommendation for increased follow-up and surveillance for patients having a relative cancer risk of greater than or equal to 2.

In order to measure device performance, this study specifically assessed the rates of sensitivity and specificity in a population of patients that closely resemble the intended use population. The observed results of sensitivity and specificity along with data on the prevalence of cancer in the intended use population were used to estimate 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.

While this calculation is described in mathematical terms below, it is possible to conceptually validate this model rather simply. For example, if published data indicates that the prevalence of breast cancer in the target population is 1.5/1,000, then the average "per patient" risk is 1 cancer per 667 women (1,000/1.5). If a device identifies women who have a relative risk of 2, it would identify a cohort that had a risk of 1 cancer in 333 women.

The calculation described above can be put in mathematical terms, as shown in the following formula used to calculate relative probability[6] for breast cancer.

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[6] This calculation entails dividing the conditional probability that a T-Scan positive woman will have cancer (P[C/T} in which P(T) = probability of a T-Scan positive exam and P(C)= probability of cancer in the population at large = prevalence=0.0015) by the probability that a randomly selected woman has cancer (P(C). Using Bayes theorem P[C/T]=(P[T/C]P(C))/ (P[T/C]P(C) +(P[T/C^c)(P(C^c). In this formula:

- P[T/C]=the probability that a woman will have a T-Scan positive result if she has cancer = sensitivity of the exam.

$$P_r = \frac{S_n}{S_n R_{ca} + (1-Sp)(1-R_{ca})}$$

(Formula 11.1)

In this formula, the relative probability (P_r) is a function of the sensitivity (S_n), specificity (S_p), and the prevalence of cancer in the population (R_{ca}).

In order to validate the efficacy associated with a given level of device performance, results from this study were contrasted with the current standard of care for breast cancer risk stratification in the intended use population. Specifically, the current standard for identifying patients at risk for breast cancer in the target population relies on family history of disease. The level of risk associated with family history is universally utilized for the recommendation of increased surveillance/mammographic screening before the age of 40 (Tilanus-Linthorst *et el*., 2000; Kramer and Brown, 2004) and is often the threshold of risk at which women are enrolled in high-risk surveillance and monitoring studies (Pharoah *et al*., 2000; Kramer and Brown, 2004; Tilanus-Linshorst *et al*., 2000; Kriege *et al*., 2004. O'Driscoll *et al*., 2001; Dershaw, 2000).

The National Cancer Institute reported that in a pooled analysis of 38 studies, the relative risk of breast cancer conferred by a first-degree relative with breast cancer was 2.1 (95% confidence interval (2.0,2.2)) (Pharoah *et al.*, 1997). A more recent meta-analysis of 52 epidemiological studies placed the relative risk conferred by a first degree relative with breast cancer at 1.9 (99% confidence interval (1.69, 1.91)) (Collaborative Group on Hormonal Factors in Breast Cancer, 2001).

On this basis, discussions of device efficacy with FDA (see **Appendix 11.6.3** for documentation of correspondence with the FDA on this point) have focused on the capacity of the T-Scan™ to identify risk that is equal to or greater than the risk detection standard provided by family history alone. Thus, 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. This success criterion was extensively discussed and agreed upon in a meeting with FDA on June 2, 2003, prior to the initiation of the clinical study. The minutes of that meeting describe the agreement to use relative probability as the measure of study success. Those minutes reflect that "the company intends to set a threshold of 2.0 for relative probability to demonstrate success of the clinical study" and that "FDA believes that this is a reasonable approach."

11.2.4.2 Results of Calculation of Relative Probability

Combining the per protocol results from the two Arms of the study with the measured specificity of **94.7%** (1658/1751) and measured sensitivity of **26.4%** (23/87) and utilizing the prevalence of carcinoma in women age 30-39 as 1.5/1000 women (Kerlikowske *et al*., 1993), the relative probability of a woman with a positive T-Scan™ examination having

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- ($P[T/C^c]$= the probability that a woman will have a T-Scan positive result if she does *not* have cancer= the false positive rate=1-specificity of the exam.
- ($P(C^c)$= the probability that a woman does not have cancer=1-prevalence=1=0.0015=0.9985.

cancer was **4.95** with a 95% confidence interval estimated by bootstrapping methods of (3.16 - 7.14). In other words, 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. In fact, the relative probability for breast cancer in women with T-Scan™ positivity not only exceeded the primary success criterion, but also compares favorably with the relative risk associated with other conditions (see Section 11.3.1.1 below) that are generally considered justifications for screening mammography or even the initiation of preventative measures (Kramer and Brown, 2004).

Adjusting for some variability in prevalence, due to the potential 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 P_r is 4.96. Assuming a prevalence of cancer of 2/1000 women would result in an estimated relative probability 4.94.

Furthermore, if the relative probability is recalculated using data exclusively from women under the age of 40 in the study, the relative probability based on the observed specificity of 94.7% and sensitivity of 18.9% in women ages 30 to 39 was 3.6 (with a bootstrapped 95% confidence interval of 1.43 - 6.19).

Additionally, based on all 131 cancers with available data (131% of the initially proposed sample size), the relative probability is 4.30 with a bootstrapped 95% confidence interval of (2.79 - 6.02). Thus, with 131% of the initially proposed sample size, albeit based on a population of patients some of whom did not strictly meet all eligibility criteria, the relative probability still far exceeded the primary success criterion of a relative probability of 2.0.

11.2.4.3 Additional estimates of efficacy

The data from this study can also be used to calculate the positive predictive value and odds ratio associated with the T-Scan™ examination. Complete data from both arms of the clinical study are summarized in Table 11.24 below.

Table 11.24 T-Scan™ results by lesion classification

T-Scan™	Normal	Benign	Malignant	Total
Negative	1,658 (94.7%)	245 (80.9%)	64 (73.6%)	1967 (91.9%)
Positive	93 (5.3%)	58 (19.1%)	23 (26.4%)	174 (8.1%)
Total	1,751 (100%)	303 (100%)	87(100%)	2,141 (100%)

As can be seen in the study summary table above, the prevalence of cancer in the study was 87/2141 or ~ 41/1000 women. This number is significantly greater than the actual estimated prevalence of breast cancer in the intended use population of 1.5 cancers per 1000 women. In order to more accurately represent the intended use population, the following table (Table

11.25) proportionally increases the total number of well women aged 30-39 in the Normal column to maintain the accepted ratio between well women and expected cancer cases. Thus, the well woman population is inflated from the actual 1,751 to a projected 46,383.

Table 11.25 Projected T-Scan™ results in the intended use population

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%)	58000 (100%)

The above table can be further collapsed to show cancer vs. non-cancer patients (Table 11.26).

Table 11.26 T-Scan™ results in cancer and non-cancer cases

T-Scan™	Non-Cancer Cases	Cancer Cases	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%)	58000 (100%)

The projected data in the above 2x2 contingency table was analyzed by using logistic regression to find a strong dependence of the ordered categories of non-cancer cases and cancer cases on negative or positive T-Scan™ test results, with adjusted odds ratio = 6.33 and corresponding 95% confidence interval (CI) = 3.93-10.21. These results strongly indicate that women with positive T-Scan™ exam results have substantially greater odds of having malignant lesions than women with negative T-Scan™ test results.

Additionally, resulting in the corresponding predicted probabilities:

Pr(Cancer| Negative Test Result) = 0.00117 with 95% CI = (0.00091 - 0.00149); Pr(Non-Cancer| Negative Test Result) = 0.99883.

Pr(Cancer| Positive Test Result) = 0.00734 with 95% CI = (0.00488 - 0.01102); Pr(Non-Cancer| Positive Test Result) = 0.9266.

These results indicate that approximately 1 in every 136 positive T-Scan™ results will be a cancer case.

11.2.4.4 Conclusion

The data from this study indicate that women who are positive on T-Scan™ have a probability of having breast cancer that is almost five times greater than that for a woman

randomly selected from the target population at large. In the population of 30-39 year old women, there is on average about one cancer case for every 666 women. In contrast, among T-Scan™ positive women, there is expected to be one cancer case for every 136 women.

11.3 Discussion and Conclusions

The T-Scan™ device is intended to be used as a complement to CBE in asymptomatic women ages 30-39 who do not have a palpable lesion. The section below discusses how the performance of the device in this study compares with the current standard of care in breast cancer screening.

11.3.1 Risk factors for breast cancer and relative probability

At present, women age 30-39 are only screened for breast cancer with mammography if they have a family history or other risk factor that would justify such screening. The magnitude of risk in such women is commonly expressed as relative risk. Table 11.27 below presents a list of conditions associated with increased risk for breast cancer and their relative risk.

Table 11.27 Lifetime relative risk of cancer for women with various conditions commonly used to recommend breast imaging/screening before the age of 40

Class	Condition	Relative Risk	Reference
Family History	One 1st degree relative	1.7-2.0	Pharoah *et al.,* 2000; Collaborative Group on Hormonal Factors in Breast Cancer, 2001
	Two 1st degree relatives	2.92	Collaborative Group on Hormonal Factors in Breast Cancer, 2001
	Three or more 1st degree relatives	3.9	Collaborative Group on Hormonal Factors in Breast Cancer, 2001
Genetic Factors	BRCA1	5.7	Schwab *et al*., 2002
	BRCA2	5.7	Schwab *et al*., 2002
Histological results of breast biopsy	Previous Breast Cancer	2.0-4.0	Feig *et al*., 1998
	Atypical Hyperplasia	4.0	Feig *et al*., 1998
	LCIS	5.9-12.0	Feig *et al*., 1998

As discussed above, the design of the study did not permit a formal estimation of relative risk because this study design did not provide long term follow-up. However, a related measure –

relative probability – was chosen as the final outcome measure in this study. Commonly women are sent for early screening mammography if they have one first degree relative with breast cancer. Hence, as previously noted, it was decided to use a relative probability of at least 2 as the study success criterion.

The measure of relative probability used in this study differs from relative risk in two important ways:

- Relative risk is dependent on the prevalence of the condition in the population being studied. Relative probability used in this study is based on the published data of prevalence in the population at large and independent of the percentage of cases in this particular study that were cancerous.
- Relative risk for breast cancer as measured in other studies typically is a cumulative lifetime relative risk. This study did not include long-term follow-up of T-Scan™ positive patients. Accordingly, the study does not provide significant insight regarding the extent to which women who are positive on a current T-Scan™ examination carry a higher future or lifetime risk for breast cancer. Rather, it can only be concluded that data from this study support the claim that women who are T-Scan™ positive have a substantially higher *current* risk of breast cancer than do women from the population at large. However, there is reason to believe that T-Scan™ positivity may also be associated with longer-term predisposition for breast cancer. Specifically, the strong association between T-Scan™ positivity and breast lesions (both malignant and benign) requiring biopsy indicates that the exam can identify more generalized breast abnormalities, which are statistically associated with a 2 to 5 fold risk for breast cancer (Hutchinson *et al*., 1980; Potter *et al*., 1968; Krieger and Hyatt, 1992). However, as stated above, further long-term follow-up studies will be required before the medical community can make far-reaching assessments based solely upon T-Scan™ positivity. Therefore, based upon the current data, patients should only be sent for one-time mammographic or sonographic screening following a T-Scan™ positive exam.

11.3.2 Number of mammograms required to detect one cancer

The T-Scan™ exam aims to identify a cohort of women between ages 30-39 who are at increased risk for breast cancer, but who would be overlooked by the current reliance upon family history as the primary means for the identification of risk. It is assumed that identifying women who have an above average risk for breast cancer may offer a cost effective way to allocate resources to those who are most likely to benefit.

This point can be clarified by comparing the accepted ratio between mammography screening exams and cancers detected in older women (>40) and younger women who are identified by a positive T-Scan™ exam.

As summarized in the table below (Table 11.28), population-based mammographic screening studies indicate that between 341 and 593 mammograms are performed for every breast cancer detected in women aged 40-49.

Table 11.28 Ratio of number of mammograms performed per cancer detected for women age 40-49 in various mammographic screening trials

Number of women screened	Number of Cancers	Ratio mammograms/cancer	Reference
35,896	83	432:1	Bjurstam *et al*., 1997.
4,744	8	593:1	Burhenne *et al*., 1991
8,868	26	341:1	Kerlikowske *et al*., 1993

Because the prevalence for breast cancer in women under age 40 is approximately 1.5 cancers per thousand, or 1 in 666 women, the mammogram to cancer ratio is expected to be 666:1 and thus outside the accepted range of most screening models.

In women under the age of 40, current standard of care relies upon family history as a means for risk stratification, wherein women under the age of 40 with a positive family history are directed to mammographic screening. Since family history, as described above, is associated with a risk of breast cancer that is between 1.7and 2.0 times average and thus, high-risk young women for whom screening will yield a mammogram to cancer ratio of 333-392 are also routinely screened with mammography.

A positive T-Scan™ corresponds to a breast cancer risk that is approximately 5.0 times greater than the average risk. Based on the positive predictive value of T-Scan™ (discussed above), a T-Scan™ positive woman is at a risk of 1 in 136 of having breast cancer. Assuming that all such women were subsequently screened by mammography and that the sensitivity of mammography in women age 30-39 is 70%, 194 mammograms would be performed in T-Scan™ positive women for every cancer detected. Thus, T-Scan™ positivity, like a significant family history, identifies women who fall well within the accepted yield for mammographic screening.

In conclusion, T-Scan positive patients of age 30-39 are at a breast cancer risk that is considerably greater than the average risk of women age 40-49, who are routinely screened with mammography. ***In fact, taken in terms of absolute risk, women age 40-49 are at an absolute risk of ~1 in 400 or 0.0025 (see range above from 341:1 – 593:1) while T-Scan positive patients age 30-39 are at an absolute risk of 1 in 136 or 0.0074, a risk that is nearly three time larger than the absolute risk at which annual mammographic screening is mandated by the standard of care in the United States for women aged 40-49.***

11.3.3 Stage at which cancer is detected

For "average risk" women, the only regularly used detection method is Clinical Breast Exam ("CBE") or breast self-examination (BSE). However, the sensitivity of palpation is low (approximately 10%) and most cancers discovered by palpation have been growing for approximately six years (Kopans, 2000). Thus, on average, palpable cancers are larger and more advanced in stage than are non-palpable ones.

Palpable cancers are more difficult and costly to treat than non-palpable cancers (Bjurstam *et al*., 1997; McPherson *et al.,* 1997; Skinner *et al*., 2001). The stage at which breast cancer is detected has important consequences upon the affected patient in terms of survivability, treatment severity, cost and morbidity. The clinical decision to offer a lumpectomy as opposed to a mastectomy, for example, is highly associated with lesion size and extension.

Data presented in this study indicate that primary screening of young women with the T-Scan™ system may present an opportunity to detect breast cancer earlier than would be expected with palpation alone. Notably, this study is consistent with several prior EIS studies indicating that EIS technology has the ability to detect smaller lesions ($\leq$2 cm). In this study, sensitivity for smaller lesions was 35.6% as compared with a sensitivity of 22.2% for larger lesions (>2cm). This sensitivity for small lesions is of specific value because the device is intended as a complement to clinical breast exam.

T-Scan™ results were independent of palpability in both the sensitivity and specificity arms of the study, further indicating that T-Scan™ results do not hinge upon a specific lesion size. This, for obvious reasons, is a major limitation of palpation alone, which is highly dependent on lesion size.

As discussed below, these clinical advantages are obtained with a high degree of specificity (94.7%) and a corresponding low rate of false positive exams (5.3%). This is of critical clinical import because improved detection protocols directed at younger women, and other low prevalence populations, have conventionally been confounded not by low sensitivity, but by a high rate of false positive exams.

Aggressive treatment regimens, associated with later stage tumors, have an expectedly adverse effect on quality of life ("QOL"). Women undergoing adjuvant chemotherapy or radiotherapy, for example, tend to suffer from a variety of side effects (fatigue, sexual dysfunction, cognitive dysfunction) that commonly persist for months or years after treatment (Ganz 2002; Bloom, 2004; Ahles *et al*, 2002). Hence, both the direct costs of treatment as well as QOL adjusted costs to women and society are smaller for cancers discovered at an early stage (Stage 0 or I) than at a later stage (II or above).

In addition, several recent studies indicate that younger women are considerably more vulnerable to deterioration in QOL as a result of aggressive breast cancer treatment than are older women. Younger women are, on average, more likely to suffer depression, bodily pain and a decline in social functioning (Wong-Kim and Bloom, 2004, Kroenke *et al*., 2004; Ganz *et al*., 2003) than are older women.

Data presented in this study indicate that the incorporation of a T-Scan™ screening regimen may help identify breast cancer earlier and at a smaller lesion size than the present alternative of palpation alone. The T-Scan™ exam's relatively high sensitivity for small lesions, and exam results that are independent of palpability, offer a rational complement to clinical breast exam. At the same time, the low rate of falsely positive exams is expected to generate a yield that is consistent with other commonly used clinical screening exams (see discussion below).

11.3.3.1 Anticipated workup after a positive T-Scan ED Exam

The purpose of this section is to review patient management following a positive T-Scan™ examination and analyze the consequences of false positive exams for the rate of follow-up examinations and procedures.

Thresholds for the T-Scan ED post-processing algorithm have been developed to yield high specificity and thus to generate a low number of false positive results. In order to estimate the population consequences of screening with the T-Scan ED, the expected number of ultrasound and mammography exams generated by its use were calculated as well as the number of biopsies needed to discover each cancer. This analysis is based on the following assumptions:

- The PPV of a T-Scan™ examination (described above) is one cancer case for every 136 positive examinations.
- The published sensitivity and specificity of screening mammography and ultrasound are independent of the results of the T-Scan™ examination.
- The published sensitivity and specificity of screening ultrasound in women age 30-39 are 75% and 92% respectively.
- The sensitivity and specificity of screening mammography in this age population are 70% and 90% respectively.

Results of EIS

- Of 136 positive exams, 1 woman will have cancer and 135 women will be free of disease.

Projected Impact of Ultrasound

- Of the 135 women who are false positive on EIS, 10.80 (135 x 0.08) are expected to be False Positive on ultrasound.
- Of the 1 woman who is a true positive on EIS, 0.75 (1 x 0.75) are True Positive on ultrasound.

Projected Impact of Mammography

- Of the 10.80 women who are FP on US, 1.08 (10.80 x 0.1) will be False Positive on mammography
- Of the 0.75 women who are True Positive on US, 0.525 (0.75 x 0.7) will be True Positive on mammography.

Consequences for Rate of Biopsy

- 1.61 women (1.08 + 0.525) women will be referred for biopsy.
- Of these 1.61 women, **32.6%** (0.525/1.61) will have cancer.

This percentage of cancers among women sent for biopsy of 32.6% is far higher than that currently found in the United States. Table 11.29 presents data from US centers on the percentage of cancers among biopsy cases for biopsy recommended on the basis of standard screening tests. Typically in the United States, this value ranges between 15-30%.

Table 11.29 The percentage of biopsy cases that have cancer *

Percent cancer	Reference
21%	Brown, 1995
17%	Poplack *et al*., 1999
24%	Robertson,1993
15%	Bennett *et al*., 1991
21%	Seltzer, 1992

**Only studies having a random or consecutive sample of patients included in this table.*

In summary, false positive exams are a limiting factor for all screening modalities. The costs associated with any screening technique are always highly sensitive to the False Positive Rate associated with the exam. In the case of the T-Scan ED, these costs appear consistent with, or better than the current standard of care.

Based on the results of this study, the role of T-Scan ED as a screening modality for young women can be summarized as follows:

- Women who visit their Ob/Gyn or family practitioner for a routine examination should be given a clinical breast exam ("CBE").
- Women who are positive on CBE should be followed up according to standard of care.
- Women who are negative on CBE should be examined with the T-Scan ED.
- Women who are positive on the T-Scan ED examination should be recommended for further imaging examinations, *e.g*., ultrasound or mammography. However, in all cases, the role of T-Scan™ findings in the final decision about further imaging examinations must be taken by the responsible physician in light of the full clinical information available, including patient history, patient characteristics, and results of other tests.

11.4 Conclusion

This prospective, multicenter 2,035 patient pivotal study of the T-Scan ED evaluated the sensitivity and specificity of the device for identifying asymptomatic women between the ages of 30-39 who are at increased risk for breast cancer. Sensitivity was found to be **26.4%,** specificity was found to be **94.7%**, and the associated relative probability that an exam positive woman would have breast cancer was **4.95** times greater than the average risk for breast cancer in the intended use population.

The rate of breast cancer in younger women is 1 in 217 (SEER, 1993, 2002) by age 40. However, the only breast cancer-screening procedure routinely performed on asymptomatic younger women is clinical breast exam (CBE), which suffers poor sensitivity (as low as 10% - 17%, (Kriege *et al*., 2004)), and is difficult to standardize and document. Accordingly, nearly 80% of breast cancers in this age group are self-detected (Coats *et al*.,

2001) when the mass becomes large enough to be palpated by the patient. Annual screening mammography is not generally recommended for this patient population because of: (1) its limitations in imaging dense breast tissue in younger women; (2) the minor, but repeat exposure to ionizing radiation; (3) the societal costs of performing mammograms on a large patient population with a low prevalence for breast cancer; and (4) the expense of following up the large number of false positive mammograms due to the increased false positive rate of mammography in dense breast tissue (Carney, *et al*., 2003).

Currently, asymptomatic younger women are referred for breast imaging or further testing when they are assumed to be at higher risk due to known familial risk factors, *i.e.,* a first-degree relative with a history of breast cancer. However, family history confers a lifetime relative risk for breast cancer that is only 1.9 to 3.9 times greater than the average risk. The pivotal study demonstrates that women with a positive T-Scan ED examination are approximately five times more likely to have breast cancer than average risk woman in the target population. Consequently, the risk of breast cancer is higher for women with a positive T-Scan ED examination than for women with a family history of breast cancer, who are routinely directed towards mammography or ultrasound. Thus, referring women with a positive T-Scan™ result for breast imaging is consistent with the current standard of care. This conclusion is further justified by the low false positive rate (**5.3%**) associated with the T-Scan™ exam. Further, the 1 in 136 risk of breast cancer in the T-Scan positive subgroup is greater than the risk of 1 in 400 for all women age 40-49, leading further concrete justification for referring T-Scan positive patients to mammography.

The primary factor associated with improved patient outcomes, both in terms of morbidity and mortality is early detection, and improved screening of at-risk women contributes to such early detection (Tilanus-Linthorst, *et al*., 2000). In younger women, early detection is of particular importance because breast cancer in this population is associated with a number of unfavorable prognostic characteristics (Shannon and Smith, 2003; Sundquist *et al*., 2002) and increased societal costs. In fact, a recent Institute of Medicine Committee report expressly identifies the need for improved breast cancer detection in all women and specifically in high-risk young women (Institute of Medicine and Nat'l Research Council of The National Academies, 2004).

T-Scan ED represents an important approach to the significant challenge of identifying high-risk women under age 40. Clinically, the T-Scan™ exam has consistently proven safe in a number of widespread studies, and is well accepted by clinicians and patients. Epidemiologically, positive T-Scan™ examination results provide a reasonable basis for referring younger women to further evaluation with mammography or ultrasound and offers an efficacious approach to population based screening of women who currently have no other practical modality for breast cancer detection.

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11.6 List of Appendices included in the PMA document

Appendix 11.6.1: Complete Study Protocol

Appendix 11.6.2: Study Case Report Forms

Appendix 11.6.3: Relevant Correspondence and Minutes of Meetings with FDA

13. Device Labeling

The labeling for the T-Scan™ 2000ED (Early Detection) consists of: (1) the labels affixed to the device and its shipping container; (2) the User's Manual; (3) the Patient Guide, which is in question and answer format; (4) the Service Manual; and (5) draft promotional material. For FDA's convenience, the same labels are appended to Section 5 entitled "Device Description".

13.1 Labels

The T-Scan ED bears 11 labels. The drafts of these labels are provided in **Appendix 13.7.1**.

13.2 User's Manual

The draft User's Manual is provided in **Appendix 13.7.2**.

13.3 Information for Prescribers

The draft Patient Guide is provided in **Appendix 13.7.3**.

13.4 The Patient Guide

The draft Patient Guide is provided in **Appendix 13.7.4**.

13.5 The Service Manual

The draft Service Manual is provided in **Appendix 13.7.5**.

13.6 Promotional Materials

The draft promotional materials are provided in **Appendix 13.7.6**.

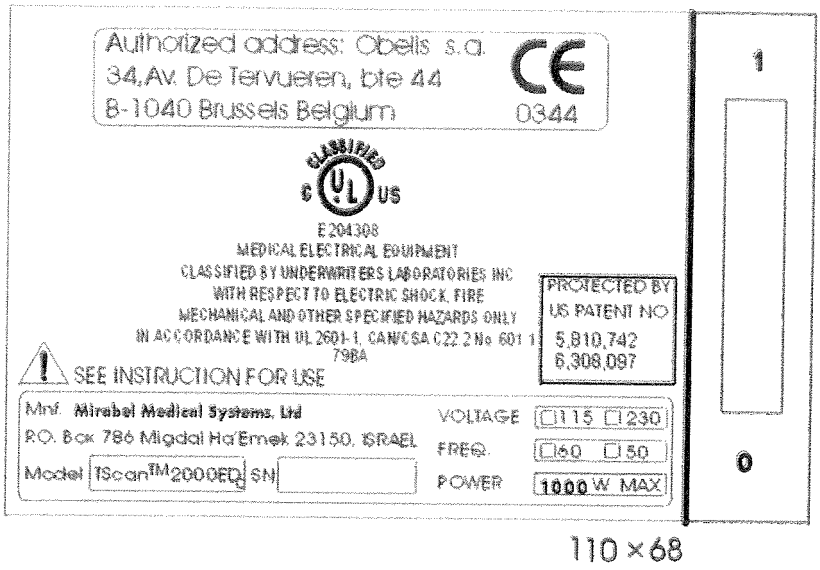
13.7 Appendices

Appendix 13.7.1 Device Labels
Appendix 13.7.2 User's Manual
Appendix 13.7.3 Information for Prescribers
Appendix 13.7.4 Patient Guide
Appendix 13.7.5 Service Manual
Appendix 13.7.6 Promotional Materials

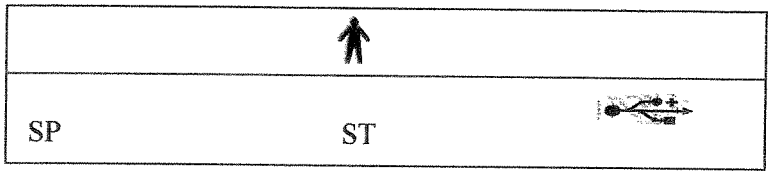
Labels

1. Cart Labels

a. System and Circuit breaker label (on back of cart)



b. Connectors label (on back of cart)



c. System name label (On front Panel)

T-Scan™

d. Screen label (On LCD monitor)

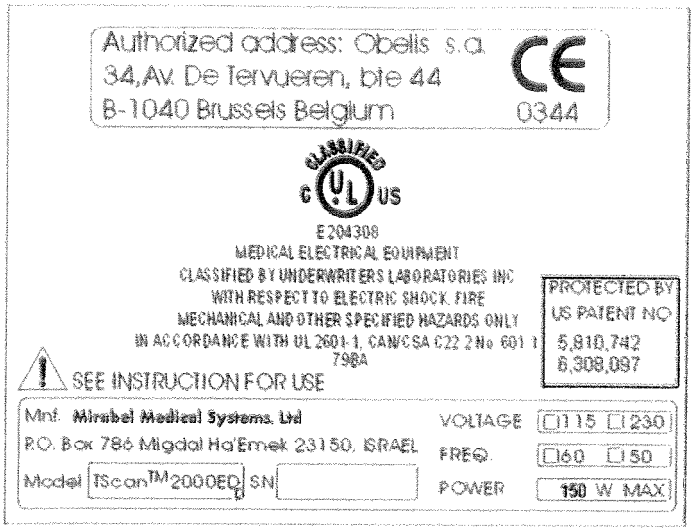
e. Transformer label (Inside cart)

Isolation Transformer Label – inside the cart

f. Company LOGO (On the side and front panel of cart)

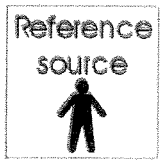
Desktop Label

g. Desktop System label (on back of device)



72×68

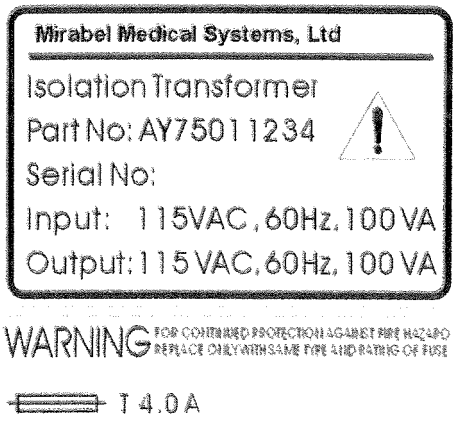
h. Connectors label (on back of device)

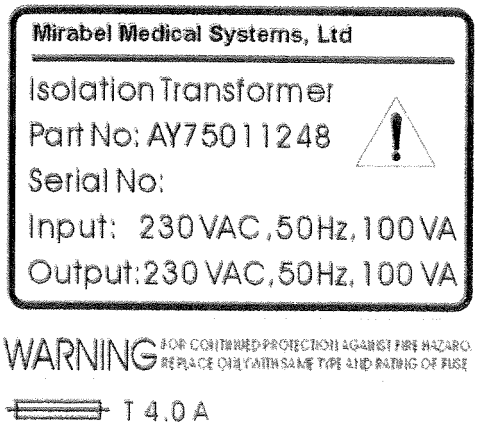


20×20

25×22

i. Transformer label (On outside surface of transformer)



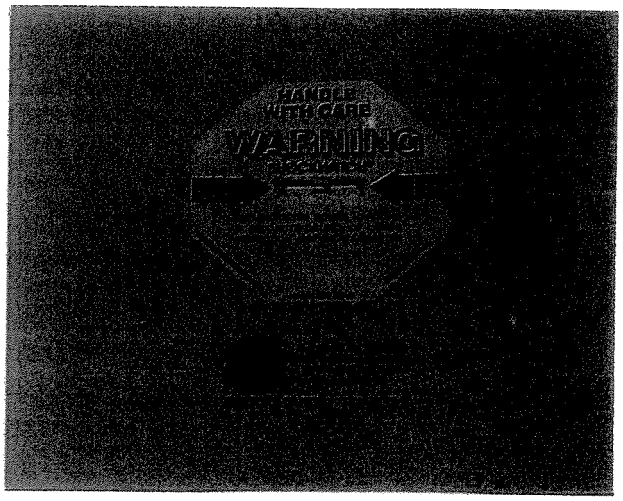


2.Package labels

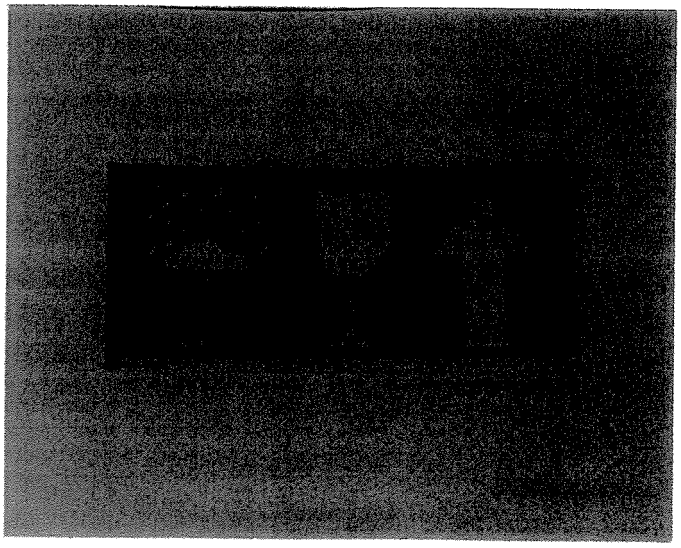
a. Security code for Israeli customs

R-382

b. Safety labels for the package while in transport



c. Direction and precautions for package while in transportation



d. System Serial Number and model number

Cart Configuration

ITEM: T-Scan™2000ED$_C$ 115V Only (Bar code) **MODEL NO**: PR75011372 **SERIAL NUMBER: XXYYZZ** (Bar code)	**ITEM**: T-Scan™2000ED$_C$ 230V Only (Bar code) **MODEL NO**: PR75011371 (Bar code) **SERIAL NUMBER: XXYYZZ** (Bar code)

Desktop Configuration

ITEM: T-Scan™2000ED$_D$ 115V Only (Bar code) **MODEL NO**: PR75011499 (Bar code) **SERIAL NUMBER: XXYYZZ** (Bar code)	**ITEM**: T-Scan™2000ED$_D$ 230V Only (Bar code) **MODEL NO**: PR75011498 (Bar code) **SERIAL NUMBER: XXYYZZ** (Bar code)

Mirabel Medical Systems Inc.'s T-Scan™ 2000ED

Information for Prescribers

Brief Device Description

T-Scan™ 2000ED (Early Detection, "T-Scan ED") is a noninvasive, radiation-free device for breast cancer risk detection in women ages 30 to 39. The device is based on electrical impedance scanning ("EIS") that maps the local impedance properties of breast tissue (Assenheimer *et al*., 2001; Scholtz and Anderson, 2000). Detection of cancer by EIS is based on the measurable differences in capacitance and resistance between neoplastic and surrounding normal tissue. Large differences in electrical impedance between malignant tumors and benign or normal breast tissue have been reported by *in-vitro* measurements on freshly excised breast tissue (Fricke and Morse, 1926; Jossinet, 1996, 1998; Morimoto *et al.*, 1990; Suroweic *et al.*, 1988).

The T-Scan ED measures and maps the local distribution of tissue electrical impedance over four frequency **[Redacted]**, by applying an electrical signal (approximately 1 volt) via a Signal Transmitter that is held in the hand of the patient contralateral to the breast being examined. The resulting electric currents are detected by a Surface Probe placed on the breast being examined. A conductive (ultrasound) gel, which is not supplied with the device, is applied to the Signal Transmitter, the Scan Probe, and the breast.

For each frequency, the electrical capacitance and conductance at each of 64 sensors on the Surface Probe are computed. The T-Scan ED analyzes the multi-frequency data and produces a binary outcome of negative (normal tissue) or positive (some tissue suspected of being malignant, *i.e.,* suspicious). It utilizes data from 18 sectors (9 sectors per breast) using **[Redacted]**. The device displays nine conductance images per breast (one of each area scanned), which are used only to evaluate the quality of the contact between the probe and the breast. A green vertical bar between the images of the left and right breasts indicates whether the user is applying appropriate pressure.

For each sector and frequency, the measured conductivity and capacitance values are averaged over all sector pixels. The set of resulting averages is analyzed by an algorithm that was developed with data from a subset of patients in the pilot study. Underneath the figure of both breasts, the device displays a green solid horizontal line if the result is negative or a red hatched line if the result is positive. The device thus automatically and unambiguously indicates whether the tissue is normal or suspicious. The technology presents no known risk.

The T-Scan ED, in combination with clinical breast examination ("CBE"), helps identify young women who are at increased risk for breast cancer but for whom no other appropriate early detection modality exists. However, the T-Scan ED does not show or

identify the location of any suspicious lesion within the breast. A woman who is T-Scan ED positive should be referred for breast imaging with mammography or ultrasound.

Indications For Use

The T-Scan™ 2000ED is indicated for use as a complement to CBE in asymptomatic women who are age 30 to 39, inclusive. The device detects differences in the electrical impedance of tissue that are associated with an increased risk of breast cancer. A positive T-Scan ED result provides physicians with additional information to guide a recommendation regarding further breast examination, *e.g.,* mammography or ultrasound.

Contraindications

T-Scan ED should not be used on:

- Pregnant women; or
- Women with implanted electrical devices, *e.g.*, cardiac pacemaker.

Warnings

The T-Scan ED is indicated for use as a complement to CBE in women ages 30 to 39 who do not have palpable lesions, family history of breast cancer, or known genetic risks of breast cancer ("asymptomatic women"). This device does not replace conventional methods of detecting or diagnosing breast cancer, *i.e.*, CBE, mammography, MRI, ultrasound ("US"), or biopsy evaluation, when appropriate.

The effectiveness of the T-Scan ED in identifying the risk of breast cancer in women who have palpable lesions identified by CBE, family history of breast cancer, or known genetic risks of breast cancer has not been studied. The T-Scan ED is not a substitute for breast imaging, *e.g.,* mammography or ultrasound, in symptomatic women and/or women of above average risk.

Precautions

- Patients with open or incompletely healed skin wounds over the areas to be examined should be treated with caution to avoid infection. If contamination with bodily fluids is suspected, thoroughly disinfect the scan Surface Probe using 96% ethyl or isopropyl alcohol.

- The user of the T-Scan ED cannot identify where the suspicious tissue is located in the breast. Further breast examination, such as mammography or ultrasound, is necessary to localize the suspicious tissue.

- The T-Scan ED has not been tested on lactating women, women who have undergone chemotherapy, or women with recent biopsies. Physicians should interpret exam results from such women with care as their reliability has not been established.

- The patient's physician should evaluate the T-Scan ED results in conjunction with other clinical information, such as patient history, patient characteristics, and the results of other tests, in determining the appropriate management for that patient.

- Use of the T-Scan ED is limited to medical professionals who have been trained in the use of the device for identifying women at higher risk of breast cancer.

- The T-Scan ED must be used only in accordance with the User Manual, which is provided.

- In order to prevent potential injury, do not remove covers or panels of the T-Scan ED.

- Do not attempt to modify or repair the T-Scan ED. Installation and servicing should be performed by qualified service personnel only.

- The T-Scan ED patient contact surfaces should be thoroughly cleaned between patients. A soft material (cloth, paper towel, or alcohol wipe) and alcohol should be used to thoroughly clean the entire surface of the scan probe of residual gel or conductive material after each examination. Failure to do so can result in the Surface Probe producing inaccurate recordings.

Adverse Events

No adverse events have occurred in any study using the T-Scan™ family of EIS devices, including the T-Scan ED.

As with any screening device, unknown factors or influences can produce misleading results.

Clinical Studies

Overview of Clinical Studies

The T-Scan ED exam is intended to be used for identifying women between the ages of 30 to 39 who are at increased risk for breast cancer, but who may be overlooked by the current reliance upon family history as the primary means for the identification of risk. Two clinical studies have been conducted to evaluate the clinical safety and effectiveness of the T-Scan ED. A pilot study was conducted in order to evaluate the feasibility of combining a post-processing algorithm with the core EIS technology. A pivotal trial was conducted in order to obtain reliable estimates of sensitivity and specificity and, in turn, estimate the device's ability to detect tissue changes and identify breast cancer risk in the target population. Under the current standard of care, women with a relative risk of 2.0 or more are considered "at risk" and offered additional imaging, greater surveillance, and enrollment in specific management protocols. Thus, the primary endpoint of the pivotal study was to determine if a woman who is positive on a T-Scan ED exam is at a risk for

breast cancer that is 2 or more times greater than the expected risk in the general target population.

Pilot Study

The purpose of this pilot study was to determine if the core EIS technology, coupled with an experimental processing algorithm could, achieve a high (>90%) level of specificity, and to collect data for further development of an algorithm offering high specificity and clinically useful sensitivity.

The pilot study was conducted at 14 medical centers on a total of 1,708 women ranging in age from 17-77 years. Patients presenting at the medical center for screening mammography, ultrasound, annual gynecological exam or for breast biopsy were offered enrollment in the study. Patients who enrolled in the T-Scan ED study followed their regular clinical course regardless of T-Scan ED result.

Sensitivity of the device was estimated by comparing the rate of T-Scan ED positive results with the number of biopsy proven cancers. In the Specificity Arm, it was assumed that women did not have breast cancer if (1) all other performed screening examinations (CBE, US, and/or mammography) were normal; (2) they had lesions that were either not deemed sufficiently suspicious to warrant biopsy; or (3) they had biopsy-proven benign lesions. The resultant T-Scan ED specificity estimates were 92.6% for screening cases and 93.9% for benign/biopsy cases with a corresponding sensitivity of 11.5% for biopsy proven cancers.

Data from the pilot study indicated that it was possible to construct an algorithm that could operate at a high level of specificity. This formed the basis for development of the EISYS algorithm.

Pivotal Study

Overview

A multicenter, prospective study was conducted to evaluate the association between T-Scan ED 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 and the other arm estimated sensitivity of the T-Scan ED. All per protocol cases included in the Specificity Arm of this study were in the intended use population of women age 30-39. In the Sensitivity Arm, however, an expanded age range (30-45) was studied in order to allow more expeditious accrual of patients while maintaining breast tissue characteristics that are consistent with the target age range. The primary endpoint of the study used the estimates of sensitivity and specificity to calculate the probability that a woman who is T-Scan ED positive has cancer relative to a randomly selected women from the population at large, or the “relative probability”.

Specificity Arm

Study subjects in the Specificity Arm of the study consisted of 1,950 women enrolled at 14 clinical sites in Israel and the U.S., who had no breast cancer related signs or symptoms and who visited their Ob/Gyn or breast center for an annual physical exam. Candidates were women age 30 to 39 who were not pregnant.

Subjects were excluded from this study if prior to enrollment they had previous cosmetic surgery, breast biopsy or surgery within three months (90 days) of the exam, previous breast fine needle aspiration within 1 month (30 days) of the examination, were breast-feeding within the previous three months, had an electrically powered implanted device, *e.g*. pacemaker, had a history of or currently undergoing chemotherapy, or had known breast cancer.

All patients had a CBE by a qualified examiner (typically the referring physician or the principal investigator). Since all women did not present signs or symptoms of breast cancer, it was assumed that all women in the Specificity Arm of the study were free of breast cancer.

Of the 1,946 women enrolled, 1,933 ED examinations were completed, of which 1,751 were completed per protocol.

Results

The overall specificity for the per protocol population in the Specificity Arm was **94.9%**. This specificity was unaffected by presence of a palpable mass, menopausal status, hormone use, family history of breast cancer or racial/ethnic group. It was significantly related to bra cup size being lower (although still above 90%) for larger breasted women.

Safety

There were no reported cardiac, neurological, dermal, thermal or allergic reactions or adverse events, nor any reports of patient discomfort. This was consistent with 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 application.

Sensitivity (Biopsy) Arm

The Specificity Arm was designed to estimate specificity in the intended use population, *i.e.*, women age 30 to 39 without a palpable mass. However, in designing the Sensitivity Arm, it was impracticable to limit the study subjects to the intended use population. Consequently, an enriched population, including women age 30 to 45 and women with palpable lesions, was studied.

Study Design

In this arm 384 women were enrolled at 16 clinical sites in Israel and the United States. Subjects were between the ages of 30 and 45 (inclusive) who had a suspicious breast lesion based on the results of a CBE, mammography, ultrasound or MRI and had been referred for breast biopsy.

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 and all women in the Sensitivity Arm were scheduled for breast biopsy. The exclusion criteria were identical between the two arms of the study, except that women with a palpable mass were included in the Sensitivity Arm.

Of the 380 women enrolled, 349 had completed T-Scan ED exams and biopsy results, of which 284 had exams completed per protocol (214 benign cases; 70 cancer cases).

Results

The overall sensitivity for the per protocol population with pathology confirmed cancers was 31.4% (22/70). Although not part of the intended use population, the overall specificity for the per protocol population with pathology confirmed benign lesions was also calculated resulting in a specificity of 82.2% (176/214). Neither sensitivity nor specificity for benign lesions was related to the covariates of palpability, family history, or hormone use. Specificity for benign lesions was related to bra size and age category and was higher for younger women and those with smaller bra cup sizes. Sensitivity showed a statistically non-significant relationship with cancer size and was higher for smaller cancers.

Safety

There were no reported cardiac, neurological, dermal, thermal, allergic reactions or adverse events, nor any reports of patient discomfort.

Combined Results of the Two Arms of the Study

The measured results of sensitivity and specificity along with data on the prevalence of cancer in the intended use population were used to estimate 'relative probability", *i.e.*, the probability that a woman who is T-Scan ED positive will have breast cancer relative to that of a woman randomly selected from the population at large. The following formula was used to calculate relative probability for breast cancer:

$$P_r = \frac{S_n}{S_n R_{ca} + (1\text{-}Sp)\,(1 - R_{ca})}$$

Thus, the relative probability (P_r) is a function of the sensitivity (S_n), specificity (S_p), and the prevalence of cancer in the population (R_{ca}).

Results

Combining the per protocol results from the two arms of the study with the measured specificity of **94.9%** (1662/1751) and measured sensitivity of **31.4%** (22/70) and utilizing the prevalence of carcinoma in women age 30-39 as 1.5/1000 women (Kerlikowske *et al.*, 1993), the relative probability of a woman with a positive T-Scan ED examination having cancer was **6.13** with a 95% confidence interval of (3.96, 8.90). The T-Scan ED associated relative probability for breast cancer, significantly exceeds the threshold of 2.0, and thus meets the primary study success criterion.

Additionally, the results of both the Sensitivity and Specificity Arms were combined by adjusting for a prevalence of cancer of 1.5/1000. The resultant positive predictive value indicates that approximately 1 in 110 positive T-Scan ED exams will be a cancer case.

Conclusions Drawn from Studies

The T-Scan ED device for breast cancer risk assessment in 30-39 year old, asymptomatic women is able to identify women that are associated with an increased potential for breast cancer. The data from this study indicate that women who are T-Scan ED positive have a probability of having breast cancer that is more than six times greater than that for a woman randomly selected from the population at large. In the population of 30-39 year old women there is, on average, about one cancer case for every 667 women. In contrast, among T-Scan ED positive women, there is expected to be one cancer case for every 110 women. Thus, T-Scan ED positivity, like a significant family history, identifies specific women who fall well within the accepted yield for mammographic screening. The relative probability for breast cancer in women with T-Scan ED positivity also compares favorably with the relative risk associated with other factors, *e.g.,* genetic factors and previous breast cancer, that are generally considered justifications for screening mammography or even the initiation of preventative measures.

Patient Selection and Treatment

Patient selection should be based on the Indications for Use, Warnings, and Precautions listed above.

Patient Counseling

Patients undergoing T-Scan ED examination should be told that the current risk of breast cancer in a woman in her thirties who does not have a palpable lesion, a family history of breast cancer, or a known genetic risk factor is approximately 1:666. The current risk for women in that category who have a positive T-Scan ED result is 1:110. In other words, the risk of breast cancer is six times higher in asymptomatic women with positive T-Scan ED results than the average asymptomatic woman their age.

However, women who are T-Scan ED positive should be reassured that this result does not mean that they have breast cancer and, in fact, the chances are only 1:110 that she does have breast cancer. It only means that their electrical measurements are outside the normal range for a woman their age. Such abnormal measurements can occur because of a variety of factors. Two such factors that were identified during the clinical study were benign breast pathology and differences in the tissue composition of the breast (large breasted women were more likely to have false positive exams than were small breasted ones). T-Scan ED positive women should be reassured that their doctor is recommending further follow-up to determine if they have breast cancer only because they are at higher risk for breast cancer and not because of any specific pathology.

Women who have positive T-Scan ED results but whose subsequent mammograms or ultrasound examination do not detect any lesions are considered to be at average risk for

breast cancer. These women, like other average risk women their age, should continue to have T-Scan ED examinations after each CBE.

Conformance to Standards

The T-Scan ED conforms to IIEC 60601-1, IEC 60601-2, ISO 9001:2000, ISO 13485:1996, IEC 601-2-10:1987, and IEC/62/61814:1998.

How Supplied

The T-Scan ED is available in two models: a desktop model ("T-Scan ED_D") and a cart model ("T-Scan ED_c"). The user must connect the components of the device after removing them from the packaging; the device is then functional once it is plugged into a main outlet, and the "start-up" menus are complete.

A commercially available ultrasound (conductive) gel is required. Gel is not supplied with the device.

Clinical Use Information

EIS Examination

The physician places the T-Scan ED device at the head of the examination table on which the patient lies supine. To perform the scan, the physician first puts conductive gel on the metal Signal Transmitter and then places the transmitter in the palm of the contralateral hand to the breast being examined, *e.g.*, the transmitter should be patient's left hand when the right breast is examined.

The physician uncovers the breast and applies a thin layer of conductive gel to the breast and Surface Probe. The physician then places the Surface Probe on the nipple of the breast and presses the "START" button on the back of the probe. This initiates the scanning procedure, allowing the physician to see the real-time image on the monitor display and ensure good contact prior to recording. Once an adequate image has been obtained, the physician makes the first recording by depressing the "RECORD" button on the back of the probe. After the first (nipple) sector is recorded, a graphic on the T-Scan ED display monitor and an audible signal indicate that the sector recording is complete. A colored line on the T-Scan ED monitor designates the location of the next sector to be recorded. Nine sectors per breast will be recorded, using the same process and following a predetermined pattern around the breast. Once the first breast is fully scanned, the T-Scan ED device will prompt the physician to begin scanning the other breast.

The physician then asks the patient to shift the Signal Transmitter to her other hand and begins scanning the other breast. The post-processing algorithm then analyzes the accumulated data in real time and displays, below the figure of both breasts, a horizontal

green, solid line for a negative (normal) exam or a horizontal, red, hatched line for a suspicious exam (outside the normal range).

Cleaning and Disinfection Instructions

- Using a lint-free cloth or paper towel, remove the gel from the Scan Probe and Signal Transmitter.
- Wipe the Scan Probe and Signal Transmitter with a clean cloth soaked in 96% alcohol.
- Visually inspect the Scan Probe and Signal Transmitter to ensure cleanliness.
- Air dry the Scan Probe and Signal Transmitter for a few minutes.

WARNING!

Failure to CLEAN and DISINFECT the probe can result in inaccurate readings and/or the transfer of contaminants between patients.

Patient Guide

Patients should be given a patient guide, which is in the form of questions and answers, prior to their T-Scan ED examination.

CAUTION: Federal Law restricts this device to sale by or on the order of a physician.

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Frequently Asked Questions about T-Scan™ 2000ED (Early Detection)

What is the T-Scan ED?

The T-Scan ED is a medical device that measures the flow of electricity across breast tissue by means of a probe that is placed on nine areas on each breast. Studies indicate that certain patterns of electricity flow across the breast may indicate a higher risk for breast cancer.

Why do I need a T-Scan™ exam if my physician did not find any lumps in my breasts during my clinical breast examination?

The T-Scan ED is designed to detect breast tissue abnormalities before a lump is large enough to be detected by clinical breast examination ("CBE") in women who are younger than the recommended minimum age for annual mammograms. The T-Scan ED can sometimes identify women who are at increased risk for breast cancer even though they do not have palpable lesions. Your doctor can use this information to decide whether to refer you for further breast examination, including a mammogram, ultrasound, or other breast imaging exam.

Why do I need a CBE if the T-Scan ED detects abnormalities that are smaller than lumps detectable by CBE?

A T-Scan and a clinical breast exam are complimentary to one another and do not substitute each other. A clinical breast exam is used to detect any lumps that may develop in breast tissue. The T-Scan, on the other hand, is used like a blood test searching for potential signs of increased risk for breast cancer. A clinical breast exam is able to specifically localize a lump should there be one. A T-Scan exam is not designed to localize a specific lump, but only to inform you and your physician that you may be at increased risk and may want to consider further screening.

Can I have a T-Scan™ exam instead of a mammogram or other imaging study?

No. The T-Scan™ does not replace mammogram or any other breast cancer detection modality. If you are above 40, or your doctor told you that you need a mammorgram, a T-Scan™ cannot be done instead.

If I have a normal result on my T-Scan™ exam can I be certain that I will not have breast cancer?

No. Unfortunately, no modality is perfect in detecting breast cancer. While studies show that the T-Scan™ exam finds tissue changes that indicate an increased risk for breast cancers, the device might miss certain changes, or even cancers. If you have a negative T-Scan™ exam and you are under age 40, you have a chance of about 1 in 600 of still having breast cancer.

If I have a abnormal T-Scan™ Exam, does it mean I have breast cancer?

No. T-Scan™ helps identify breast tissue that has certain characteristics that are associated with a higher risk of breast cancer. Thus, a positive T-Scan™ exam requires further breast examination to determine if you have breast cancer. Even with a positive T-Scan™ result, studies show that a woman's risk for having breast cancer may be as low as 1 in 100.

Do I need to make any special preparations before the exam?

No. No special preparations are necessary prior to a T-Scan™ exam.

How is the exam conducted?

During a T-Scan™ exam, a small electric signal is introduced to your hand through a wand-like cylinder that you hold. Most patients do not feel the signal at all. Some patients may feel a tingling in their fingers. The signal then travels up the muscles of your arm and across the muscle which lies behind your breast. A surface probe, which looks and feels like an ultrasound transducer, is then placed on the surface of your breast. By measuring the flow of the signal between the muscle and the measuring probe, the system isolates your breast tissue and analyzes the electrical flow across it.

Does the exam hurt?

No. More than 10,000 T-Scan™ exams have been performed to date, without any reports of pain during the exam. The exam feels similar to an abdominal ultrasound exam.

How long does the exam take?

A typical T-Scan™ exam takes less than 10 minutes.

When do I get my results?

The T-Scan™ exam provides you with an immediate result at the end of the exam. The exam is either "normal" which means that your exam is consistent with average results or "suspicious" which means some variation exists between your result and the average result. *Again, a "Suspicious" T-Scan™ exam does NOT mean you have breast cancer, it simply means that additional breast cancer imaging may be recommended.*

If I or my doctor find a lump in my breast, can I have a T-Scan™ exam to check if the lump is benign?

No. The T-Scan™ exam can not determine if a lump is benign. The standard of care is that every lump, or other breast abnormality, should be followed up by breast imagining. If you find a lump, you should contact your doctor who will help you decide whether further breast examination is warranted.

Draft Promotional Material

Introducing T-Scan™ 2000ED (Early Detection)

"State of the Art Breast Cancer Screening For Women Under 40" ™

Mirabel Medical has developed a revolutionary system for detecting breast cancer in young women. Based on **Electrical Impedance Scanning ("EIS")**, the **T-Scan™ 2000ED** (Early Detection) is used in conjunction with **CBE** in an age group for which other screening methods are less effective or limited.

The unique benefits of the T-Scan ED *include*

- Rapid training
- Safe and radiation-free
- Painless exam
- Simple 5-minute procedure
- Real-time imaging
- Immediate results
- Portable

EIS Technology

Electrical Impedance Scanning involves the measurement of capacitance and conductivity levels of breast tissue, producing a real-time gray-scale image of differences in impedance measured over a wide range of frequencies.

Differences in electrical impedance properties between normal/benign and malignant tissue were identified in the 1920's.[1] Malignant tissue differs from normal breast tissue in electrical properties because of differences in water and electrolyte content, changes in membrane permeability, and orientation and packing density of cells.[2] The potential for these electrical differences to be used in cancer detection was widely recognized and investigated i*n vitro*[3-6] and *in vivo*.[7,8]

Mirabel Medical's **T-Scan™ 2000** (formerly TransScan™ and was manufactured in 1993) was the first FDA-approved device to make use of these principles for clinical discrimination of benign from malignant lesions. Based on data from an international, multicenter trial, the **T-Scan™ 2000** received approval from the FDA in April 1999 for use as an adjunct to mammography.

Given that breast tissue density does not adversely affect **EIS**, a system based on this technology is ideal as a screening tool for young women. When used in conjunction with **CBE**, results are optimal. Because results of **EIS** exams are independent of those of **CBE**, the combination of the two tests has the potential to increase detection of carcinomas.

Unlike MRI, nuclear medicine, or ultrasound, **EIS** is inexpensive, easy to learn and perform, and its use need not limited to specialized radiology clinics. The new generation of **T-Scan™** technology, **T-Scan ED**, has the potential to be used as a widespread, community-based screening tool to identify women at high risk of having breast carcinoma.

Limitations of Other Screening Modalities

Breast cancer is the most common nonskin-related malignancy among women in the western world, and its incidence is increasing. Currently, mammography is recognized as the "gold standard" for breast cancer detection. However, mammographic sensitivity and specificity are low for some segments of the population, in particular, for young women and those with dense breast tissue. Ultrasound and MRI may potentially be used for screening in

younger-aged women. However, MRI is expensive and invasive. Ultrasound requires considerable user training and experience, and its use in screening results in a low PPV for biopsy. Currently, the only screening tool generally used for young women is clinical breast exam (CBE). However, **CBE** has low sensitivity and a high rate of false positive results relative to mammography.

MAMMOGRAPHY

In the United States, annual mammographic screening for breast cancer begins at age 40. The only women under the age of 40 routinely sent for mammographic screening are those considered to be at high risk owing to family history and/or genetic factors. Mammography is not recommended for screening in young women because of its reduced sensitivity and specificity in dense breast tissue[9-14] and concern about increased lifetime exposure to radiation.[15,16] As with the overall population of women, the incidence of breast cancer in young women also is increasing.[17,18] Breast carcinoma, when it does occur in young women, tends to be more aggressive than that in older women[19-23] and, consequently, its early detection may be of particular importance. Indeed, the more aggressive nature of breast cancer in young women indicates that screening could result in a greater impact in reducing mortality in this cohort if it were conducted at shorter intervals.[24] However, because of current screening guidelines, many cancers developing among young women are not discovered until these women reach the age at which screening is routinely conducted.[25]

ULTRASOUND

Recently, some investigators have reported results of studies that indicate the use of ultrasound as a potentially useful screening tool for women with dense breast tissue for whom mammography is ineffective. Two studies[26,27] have investigated results of ultrasound examinations administered to women with dense breasts that had normal mammography and no palpable finding on CBE. One disadvantage of using ultrasound for cancer detection is that it is largely carried out in specialized imaging centers. Unless a woman goes to a radiological center, she does not routinely have access to breast ultrasound. In addition, ultrasound examination is highly operator dependent. To be efficient and effective, the operator needs considerable training and practice. Another disadvantage is the high rate of false-positive results. The positive predictive value (PPV) of biopsies based on ultrasound results alone was only 13.6% and 10% for the above-mentioned studies. Even worse results were obtained in a study on ultrasound-guided biopsy of 805 women with lesions visible only on sonography.[28] It has been noted that the use of ultrasound as a screening tool for women with dense breasts will depend, in part, on achievement of acceptable false-positive rates.[29]

MRI AND SCINTIGRAPHY

Currently, MRI suffers from the limitations of high expense, invasiveness, reduced sensitivity for small carcinomas and DCIS, and reduced specificity, in particular, as a result of hormonal factors. Scintigraphy also is limited by expense, invasiveness and reduced sensitivity for small carcinomas. Moreover, it exposes women to radiation. Finally, MRI and scintigraphy must be performed in specialized centers, using expensive, specialized equipment and using clinicians with highly specialized training. Currently, these exams may not be suitable for widespread, population-based screening.

CBE

At the present time, **CBE** is the principal method for general breast cancer screening in women under the age of 40 and for many women aged 40-49. Yet **CBE** has low sensitivity relative to mammography, detecting only about 10%-15% of the carcinomas identified by mammography.[30,31] Furthermore, **CBE** tends to detect cancers at a later stage than those detected by mammography.[32-34] In addition, **CBE** has a high rate of false-positive results[35], although some authors report acceptable false positive levels.

Consequently, a need exists for a breast cancer screening modality for young women that avoids some of the drawbacks of other modalities. T-Scan ED fulfills that need.

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T-Scan ED
User Manual

\\\DC - 68106/0001 - 2156426 v1

Overview of Operating Instructions

1. Turn on the master switch located at the upper right of the control panel, by pressing for 5 -10 seconds. For the Desktop model, switch on by pressing the **Power** button on the UPS unit.
2. At the **Login Screen**, select a **User Name**. Enter a **Password**. Press **OK**; the **Patient List** screen will then appear.
3. Enter the patient's personal data or select an existing patient from the list.
4. To perform a new exam on an existing patient you must complete the clinical breast examination ("CBE") result and pregnancy status using the **UP/ DOWN** keys. Click on **NEW SESSION**, bottom left corner of menu. To replay previous exam, press **VIEW**; the **Examination Screen** appears.
5. Position the patient in a supine position with a pillow under her right shoulder and with her right hand above her head.
6. Apply ultrasound or a water based massage gel to the signal transmitter (source electrode) and place it in the patient's left hand.
7. Apply the gel to the surface probe and right breast.
8. Press the **START/STOP** button on the surface probe. Position the surface probe on the right nipple and manipulate to dispel any air bubbles, which appear as black spots on the screen. A solid green line indicating successful contact appears between the Right and Left Breast images. The higher the line, the better the contact.
9. When the system is **Ready to Record**, a message will appear in the sector being recorded and a green outline will appear around this sector. Press the **REC** button on the surface probe and hold the surface probe steady until recording is finished. An audible beep will be sounded and the **Recording** message at the bottom left of screen will change to **Idle**. Repeat recording if error message appears.
10. The system will prompt the user regarding the examination sequence by outlining the next sector with a yellow line. Always ensure that the surface probe is positioned in the appropriate anatomical sector.
11. After completing the right breast (there is no need to press **STOP** on the surface probe), reposition the patient with a pillow under the left shoulder with her left hand above her head.
12. Apply more gel to the signal transmitter and transfer it to patient's right hand.
13. Apply more gel to the surface probe and left breast.
14. Repeat steps 8 -10.
15. Wipe the surface probe and electrode with a paper towel. Clean both with a solution containing at least 96% alcohol.
16. Note the overall Electrical Impedance Scanning ("EIS") status of the breasts, as indicated by a green solid or red hatched line beneath the image. A green line indicates that EIS measurements are within a normal range. A red hatched line indicates that further evaluation is recommended.

17. If a printout is desired, click on the **Print** icon on the left side of screen.

18. Press the **Patient List** icon to select/enter a new patient. Press **Logout** to exit the application.

Table of Contents

Chapter 1

Information for Clinical Use

Indications for Use

The T-Scan ED is indicated for use as a complement to clinical breast examination ("CBE") in asymptomatic women who are age 30 to 39 with a negative clinical breast examination ("CBE") and a negative family history for breast cancer. The device detects differences in the electrical impedance of 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 ED evaluates women's risk of breast cancer at the time of the exam (current risk) and not lifetime risk.

Guidelines for Use

- A CBE is performed prior to the T-Scan ED examination.
- A patient with an abnormal CBE or high risk factors is referred for an additional workup, following the standard health care guidelines.
- A patient with a normal CBE is referred for a T-Scan ED exam.
- A patient with T-Scan ED exam results outside the normal range is referred for further examination by ultrasound and/or mammography.

Clinical Information

Contraindications

T-Scan ED should not be used on:

- Pregnant women; and
- Women with implanted electrical devices, *e.g.,* cardiac pacemaker.

Warnings and Precautions

Warnings

The T-Scan ED is indicated for use as a complement to CBE in women ages 30 to 39 who do not have palpable lesions, family histories of breast cancer, or known genetic risks of breast cancer ("asymptomatic woman of average risk"). This device does not replace conventional methods of detecting or diagnosing breast cancer, *i.e.*, CBE, mammography, MRI, ultrasound, or biopsy evaluation, when appropriate.

The effectiveness of the T-Scan ED in identifying the risk of breast cancer in women who have palpable lesions identified by CBE, family histories of breast cancer, or known genetic risks of breast cancer has not been studied. The T-Scan™ 2000 is not a substitute for breast imaging, *e.g.,* mammography or ultrasound, in symptomatic women and/or women of above average risk.

The T-Scan ED has not been studied on patients with implanted electronic devices, such as pacemakers. Because pacemakers detect low level electrical signals, the T-Scan ED might interfere with the pacemaker and possibly cause this implanted device to malfunction. Therefore, the T-Scan ED is not recommended for use on such patients.

Precautions

- Patients with open or incompletely healed skin wounds over the areas to be examined should be treated with caution to avoid infection. If contamination with bodily fluids is suspected, thoroughly disinfect the scan surface probe using 96% ethyl or isopropyl alcohol.
- The user of the T-Scan ED cannot identify where the suspicious tissue is located in the breast. Further breast examination, such as mammography or ultrasound, is necessary to localize the suspicious tissue.
- The safety and effectiveness of a T-Scan ED examination has not been established in pregnant women.

- The T-Scan ED has not been tested on lactating women, women who have undergone chemotherapy, or women with recent biopsies. Physicians should interpret exam results from such women with care as their reliability has not been established.
- The patient's physician should evaluate the T-Scan ED results in conjunction with other clinical information, such as patient history, patient characteristics, and the results of other tests, in determining the appropriate management for that patient.
- Use of the T-Scan™ is limited to medical professionals who have been trained in the use of the device for identifying women at higher risk of breast cancer.
- The T-Scan ED must be used only in accordance with the User Manual, which is provided.
- In order to prevent potential injury, do not remove covers or panels of the T-Scan ED.
- Do not attempt to modify or repair the T-Scan ED. Installation and servicing should be performed by qualified service personnel only.
- The T-Scan ED patient contact surfaces should be thoroughly cleaned between patients. A soft material (cloth, paper towel or alcohol wipe) and alcohol should be used to thoroughly clean the entire surface of the scan probe of residual gel or conductive material after each examination. Failure to do so can result in the surface probe producing inaccurate recordings.
- Studies have not yet been conducted to determine whether women with positive T-Scan results but whose follow-up breast examinations are negative are at increased long-term risk for breast cancer.

Safety Information

Safety-Related Symbols

Symbol	Description
	Attention: Consult accompanying documents
	Off: Power disconnection from the mains
	On: Power connection to the mains
	Type BF equipment

Dangerous voltage

Other Safety-Related Conventions

Throughout this manual, safety-related information is shaded and framed in black.

Warnings are provided when there is a potential for injury to the operator or the patient.

WARNING!

Cautions are provided when there is a potential for damage to the equipment.

! CAUTION

Safety Notes

PROPER USE OF THE PRODUCT

- The user must undergo the necessary training before using this product.
- The operating instructions must be reviewed in detail prior to use of the system.
- The installer and operator are responsible for complying with all local regulations regarding the installation and the operation of the system.

WARNING!

This equipment should be used *ONLY* in accordance with instructions for use.

ONLY qualified service personnel should complete installation and servicing.

Do not remove covers or panels, as there is a risk of electric shock.

Do not allow the system to get wet.

Do not simultaneously touch the patient and the monitor.

Do not use the equipment if the Surface probe surface is cracked or chipped.

- Technical documentation regarding the system may be purchased. However, this does not authorize non-Mirabel Medical Systems technical personnel to perform repairs.
- Mirabel Medical Systems is not responsible for repairs made without the company's express written consent.
- For safety reasons, this product should be used only with approved, original accessories from Mirabel Medical Systems or accessories supplied by a third party vendor approved by Mirabel Medical Systems.
- The user is responsible for all risks associated with using nonapproved accessories.

MAINTENANCE

The user is advised to test the proper functioning of T-Scan ED and to ensure adequate maintenance:

- Visually inspect the surface probe, cables and signal transmitter before starting an examination.
- Verify that there are no missing pixels by slowly moving a finger over the surface of the surface probe when the **START** button is pressed. Remember to hold the signal transmitter (with some gel) in the other hand. Missing pixels appear as consistently located black areas in the white print of the finger.
- Verify that there are no consistent patterns in the image by moving the surface probe gently from side to side.
- If a black/white striped pattern appears consistently in the image, please contact a service representative.
- Be sure to thoroughly clean the surface probe and the signal transmitter with a solution of 96% alcohol between each examination. This will prevent the formation of an isolating layer of dry gel.
- To change a surface probe, disconnect the system from the power supply and disconnect the surface probe connector on the connector panel, located on the back of the operation panel. For the Desktop model, disconnect the surface probe at the back panel of the computer.

Operating Safety and Protective Measures

DISCONNECTING SYSTEM IN CASE OF EMERGENCY

In hazardous situations (such as earthquake, building fire) immediately switch off the system by pressing on the UPS **POWER** switch for 3 seconds (if connected) and disconnect the system from the main power source. This disconnects the entire system from the line, resulting in the following:

- The current system program is interrupted, and
- The current operating procedures are interrupted and deleted:

Only after the cause of the hazardous situation has been remedied may the system be reconnected to the line voltage. In all other cases, *e.g.,* malfunctions, notify a Mirabel Medical Systems' customer service representative immediately.

If the system has been exposed to a building fire, notify a Mirabel Medical Systems' customer service representative prior to restarting the system to determine whether the system will require refurbishing due to fire damage.

DISPOSAL

There may be local regulations governing the disposal of this system. To avoid environmental damage and/or personal injury, consult a Mirabel Medical Systems' customer service representative prior to disposal of the system.

Electromagnetic Compatibility

This medical device complies with the recommended standard for electromagnetic compatibility ("EMC"). Please, be advised that other mobile electronic devices, *e.g.,* cellular telephones, exceed the established emission limits in EMC standards and may disrupt the functions of this medical device. Cellular telephones in the vicinity of the device should be placed in the "off" position.

Labels

Note: The CE 0344 mark for this device, as well as all other labels, can be found on the rear side of the central Unit.

This device complies with MDD regulations 93/42/EEC

MEDICAL ELECTRICAL EQUIPMENT

CLASSIFIED
WITH RESPECT TO ELECTRICAL SHOCK, FIRE, MECHANICAL AND OTHER SPECIFIED HAZARDS ONLY
In Accordance with UL 2601-1, CAN/CSA C22.2 NO. 601.1

Legal Issues

Laws and Regulations

- The T-Scan ED is CE certified, according to MDD regulation 93/42/EEC.
- To ensure the safety of operators, patients, and third parties, ensure compliance with all local and national laws and regulations. The operator must ensure that the operating instructions are readily accessible at all times.

- As the manufacturer, assembler, installer, or importer of this product, Mirabel Medical Systems is not responsible for the safety features, reliability, nor the performance of the system when:
  - The system is used in a manner other than that specified in the operating instructions.
  - Installation, upgrades, resetting, repairs and modifications of hardware, software, operating system, etc., are performed by personnel not authorized by Mirabel Medical Systems.
  - Components affecting product safety are not replaced with original Mirabel Medical Systems' spare parts.
  - Electrical wiring used to supply power to the device does not meet the specifications of VDE ordinance 0107 or local regulations.

T-SCAN ED Classification

T-SCAN ED is classified as:

- Suitable for continuous operation and
- Transportable by cart.

Software and Data

- The operating and application software used in this product is copyright protected.
- Only software released by Mirabel Medical Systems for this product may be used.
- Person-specific data are subject to data protection. Ensure compliance with all applicable laws and regulations.

Chapter 2
Introduction

What is T-Scan ED?

Welcome to the T-Scan ED system from Mirabel Medical Systems, a device that detects electrical parameters associated with malignancy.

Theory of Operation

Electrical Impedance Scanning (EIS) of the breast is based on the difference of electrical properties between normal and malignant tissues, resulting from biochemical/physiological changes typical of malignant tissue transformation. These changes involve cellular water content, the amount of extracellular fluid, membrane properties, packing density and orientation of cells. Typically, the electrical impedance of malignant tissue is lower than that of normal tissue when measured at appropriate frequencies; hence, capacitance and conductance of malignant tissue is higher.

T-Scan ED detects cancerous changes in the breast by analyzing the differences in electrical parameters associated with malignancy. The result is provided by the system and represented as a color bar.

T-Scan ED's unique potential to distinguish and detect early signs of cancer is based upon detecting these electrical changes noninvasively.

Use of T-Scan ED

T-Scan ED is used as a screening modality for young women below the recommended age for screening mammography. The Examination screen includes a 9-sector (3 x 3) image of each breast. Recordings are performed in real time. The impedance images displayed on the monitor correspond to the measurements calculated by the system.

T-Scan ED is designed for use in hospital or clinical settings, operated by trained doctors, nurses or technicians. Training is to be conducted by an authorized Mirabel Medical Systems representative.

Because T-Scan ED uses a different method of detecting malignant changes in the breast than other available methods, such as clinical breast examination ("CBE"), combining the results of T-Scan ED with those of a CBE may increase the overall sensitivity in detecting breast cancer.

T-SCAN ED Components

Figure 1: The T-Scan ED system

Principal Screens and Dialog Boxes

PRINCIPAL SCREENS OF THE T-SCAN ED

Screen	Function
Login	Use the **Login** dialog box to enter or shutdown the system (See **Figure 3**: **Login dialog box**).
Options	Use the Options dialog box to modify site (See **Figure 5: Site Information dialog box**) or examiner (See **Figure 8**: **Examiner Information dialog box**).
Patient List	Use the **Patient List** screen to enter a new patient or recall a previously entered patient (See **Figure 12**: **The Patient List Screen**).
Scan Mode	Use the **Examination** screen to acquire impedance images of the breast (See **Figure 15**: **The Examination Screen**).
Archive	Use the **Archive** screen to backup data to ZIP or CD, retrieve data from ZIP or CD or delete patients (See **Figure 22**: **The Archive Screen**).

Features

All interactions with T-Scan ED software are performed with the keyboard, trackball and the hand-held surface probe.

Icons

Icons are displayed in the top left corner of the screen. The name and use of each icon is described in the table below (see **Figure 15: The Examination Screen**)

Icon	*Icon Name*	*To*
	Patient List	Select an existing patient or enter a new patient
	New session	Start a new session
	Print	Print a report of the exam
	Logout	Logout from the application

Figure 2: Table of Icons

Surface probe

The surface probe includes a control panel of selected functions designed to allow operation from the surface probe.

BUTTONS ON THE SURFACE PROBE AND THEIR USES

Button	Uses
START/STOP	Start random scanning or stop scanning without recording
REC	Record the current sector image after appearance of the **Ready to Record** message.

Trackball

Use the trackball to move quickly around the screen. When moving the trackball, the pointer will change position on the screen. The location of the pointer is indicated by one of three symbols:

- I-shaped pointer - the I-pointer appears in a place where text can be inserted.
- Hourglass - the hourglass symbol indicates that the system is busy processing information.
- Arrow - a regular pointer showing the active area on the screen.

OPERATING THE TRACKBALL

Most of the operations with the trackball involve clicking the left button.

- Click - quickly press and release the trackball left button. A single click of the left button may select an item, in which case the item is highlighted, *e.g.,* when rerecording a sector.
- Double click - quickly click and release the trackball left button twice in close succession. It has the same function as the **Enter** button on the keyboard, *e.g.,* double-clicking on a name in the **Patient List** screen allows access to patient details.

The following operations are carried out using the right button:

- Drag – Highlight a word, group of words or skin mark, then move it, by rolling the trackball to the desired location, and release by clicking on the left button. (It is not necessary to continue to press the button while dragging.)
- In some instances, special menus are displayed by a single click with the right button.

How to Use This Manual

Organization of the Manual

This manual is organized according to the major steps in using T-Scan ED: setting up an examination; conducting an examination; storing and reviewing data; printing results. See the table below for a list of topics and their location in the manual.

STEPS IN USING T-SCAN ED

To	*See*
Set up the T-Scan ED system	Chapter **3**
Set up a new examination	Chapter **4**
Conduct an examination	Chapter **4**
Interpret the results	Chapter **4**
Archive the patient's records	Chapter **5**

Chapter 3

Getting Started

Installation

Installation should be carried out by a Mirabel Medical Systems authorized representative. The Mirabel Medical Systems representative will install the initial User Name and Password.

Working Environment

T-Scan ED should be installed in a room containing a standard examination bed. It is placed in a cart or on a table near the head of the bed. Place the T-Scan ED on the side of the bed near the patient's right hand when she is lying on her back. To conduct an exam, the operator stands on the same side of the bed as the T-Scan ED.

Starting a T-Scan ED Session

Turn on the system by activating the switch at the top right corner of the Control Panel. If a UPS unit is used, turn on the master switch located on the front of the UPS; press the button for a few seconds until the green light appears.

> Note: In order to enroll a user for the first time, when there are no listed users, call your service representative or authorized personnel.

T-Scan ED software runs under Windows™ 2000 operating system. When the system is turned on, the software automatically progresses through the startup of Windows™ 2000 (initial screen and Program Manager) and then presents the **Login** screen of T-Scan ED.

The **ON** LED surface probe should be active.

Login Procedure: Entering User Name and Password

> Note: For initial start-up of the system after installation, lift the main circuit-breaker switch at the lower right corner of the back panel.
>
> In order to enroll a user for the first time, when there are no listed users, call your service representative or authorized personnel.

When turned on, T-Scan ED initially displays the **Login** dialog box.

To log in when your User Name and Password are in the system

1. For an existing user, enter the **User Name** and **Password** (the password is case insensitive); the Field Service Specialist will provide an initial password.
2. Click **OK** (see **Figure 3**).
3. The **Patient List** screen appears, so that the user can enter the patient's data.

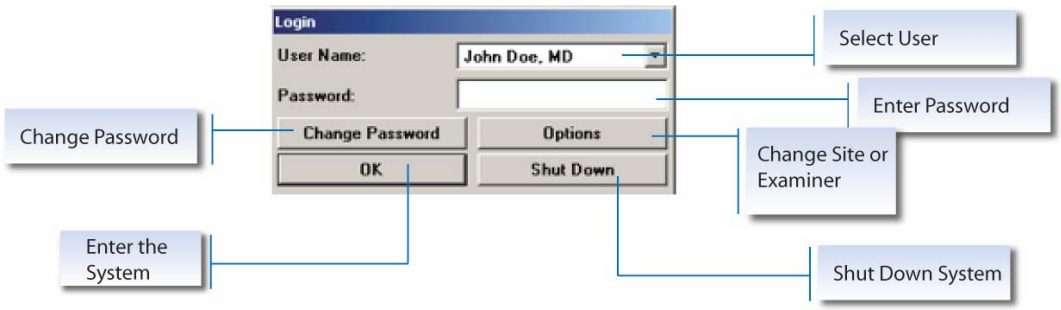


Figure 3: Login dialog box

To change the password

1. Click on **Options;** the **Change Password** dialog will appear.
2. Enter a new password. Choose a password comprised of letters and/or numbers. You may also chose not to enter a password (not recommended).
3. Enter the password twice — once in the **Password** box and then in the **Confirm Password** box.

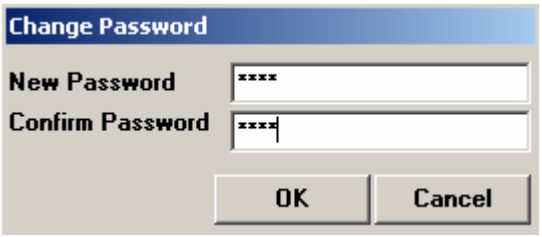


Figure 4: Change Password dialog box

Entering Site Information

To modify the information concerning an existing site or to add a new site

1 Click the Options button in the **Login** screen (see **Figure 3: Login dialog box**); the **Options** dialog box appears.

2 Select the **Site Information** tab.

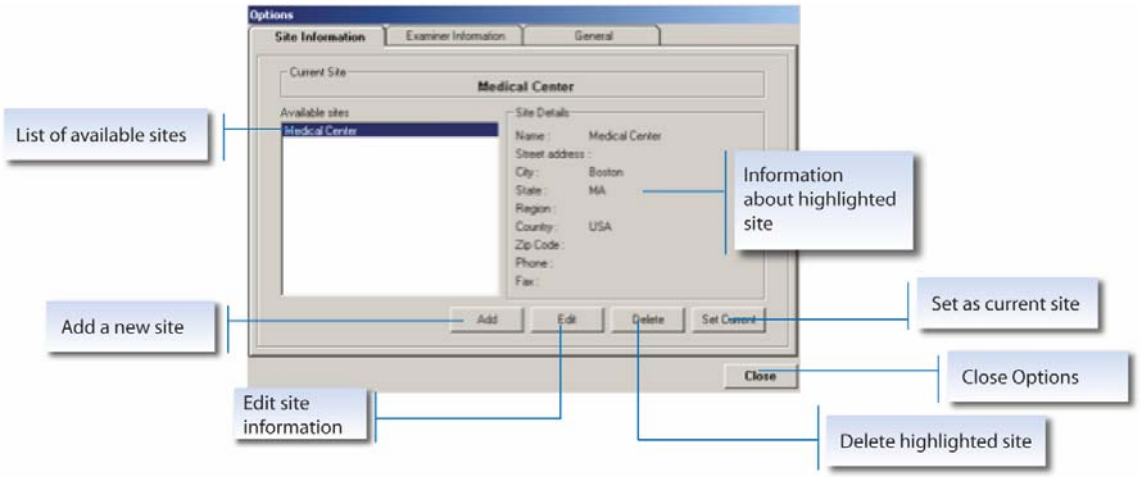


Figure 5: Site Information dialog box

To modify the information concerning an existing site

1 Press the Edit button and modify the fields.

2 Press OK to close the dialog box.

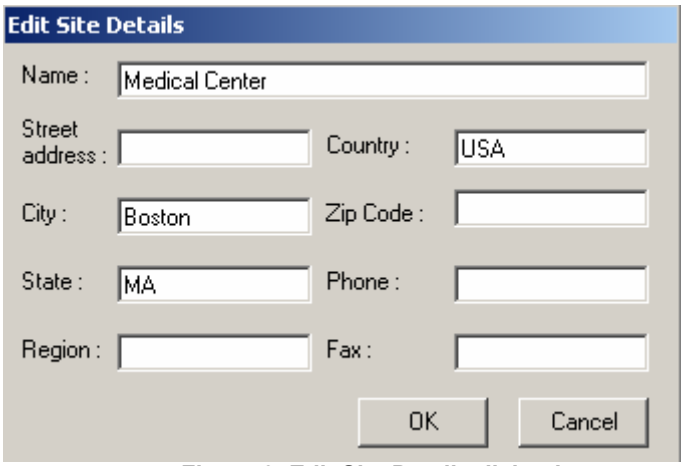


Figure 6: Edit Site Details dialog box

To add a new site

1 Press the Add button and fill in the fields.

2 Press OK to close the dialog box.

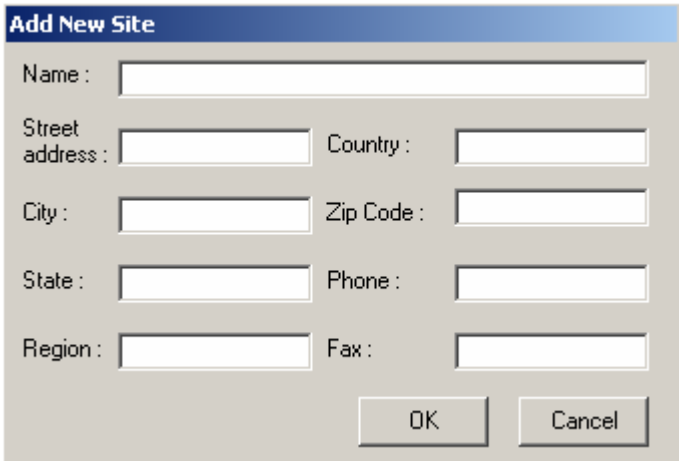


Figure 7: Add New Site dialog box

Entering Examiner Information

To modify the information concerning an existing examiner or to add a new examiner

1 Click the Options button in the **Login** screen (**Figure 3: Login dialog box**); the **Options** dialog box appears.

2 Select the **Examiner Information** tab.

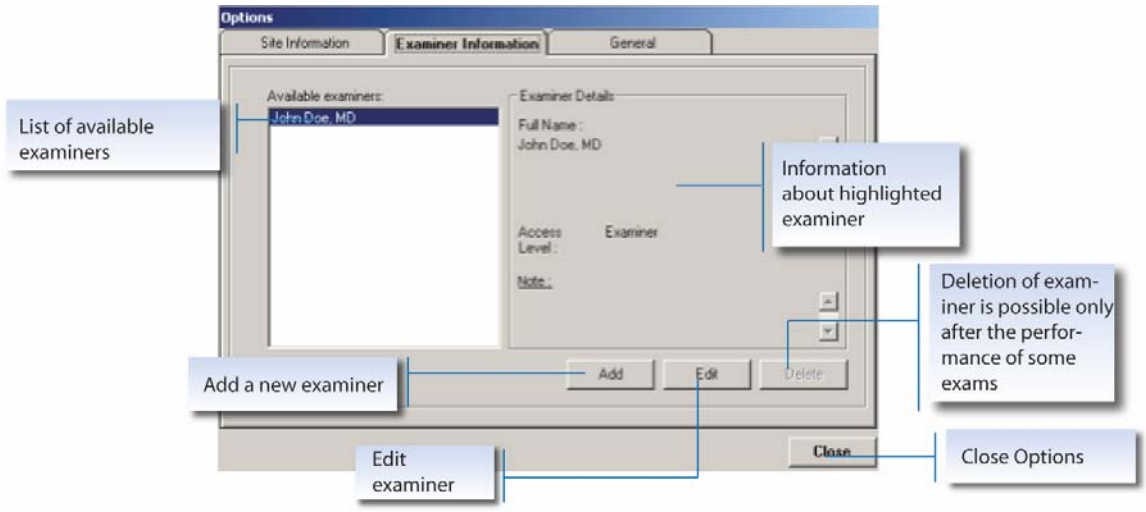


Figure 8: Examiner Information dialog box

To modify the information of an existing examiner

1 Press the Edit button and modify the fields.

2 Press OK to close the dialog box.

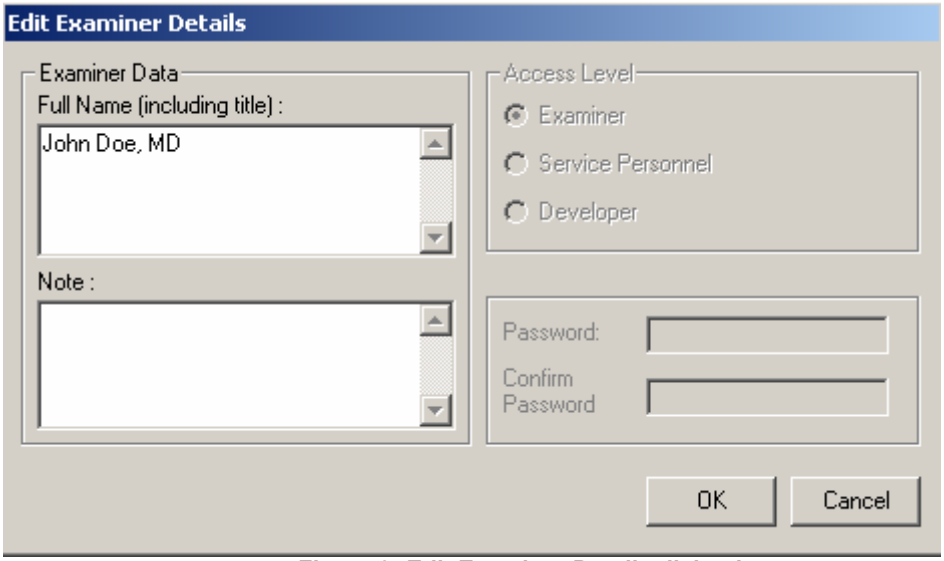


Figure 9: Edit Examiner Details dialog box

To add a new examiner

1 Press the Add button; the **Add New Examiner** dialog box appears (**Figure 10).**

2 Fill in the fields.

3 Press OK to close the dialog box.

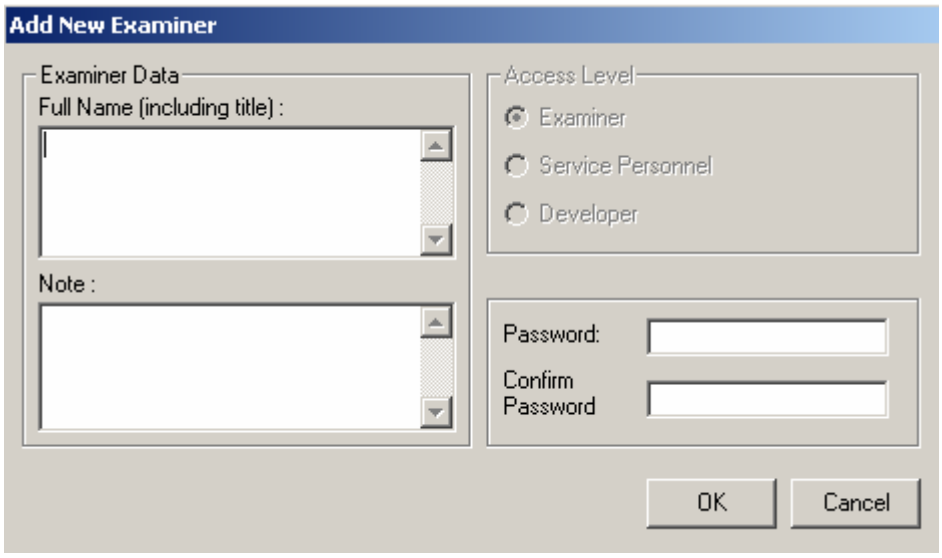


Figure 10: Add New Examiner dialog box

General Options

To Set date/time and get general information

1 Click the Options button in the **Login** screen (see Figure 3: **Login dialog box**); the **Options** dialog box appears.

2 Select **General** option.

3 Press Set Date/Time to change/set date or time and About to get details about the system.

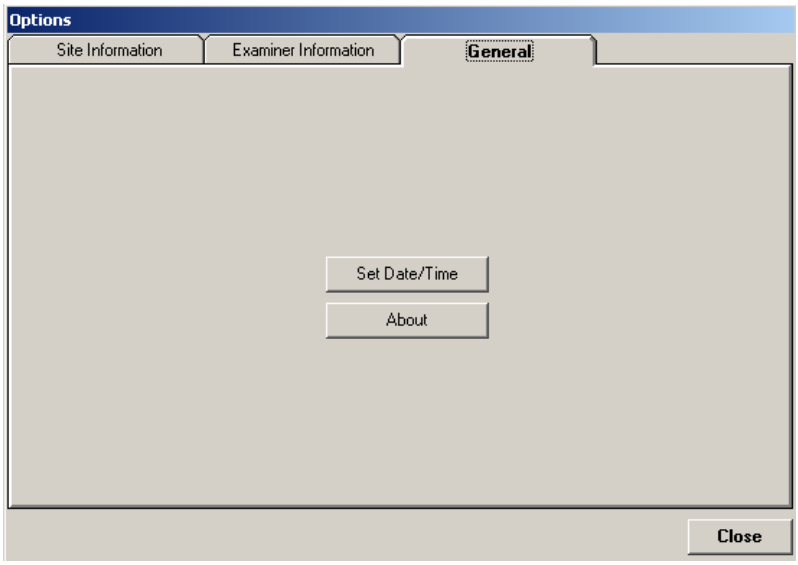


Figure 11: General Options screen

Chapter 4
Conducting an Examination

Examination Overview

A typical examination proceeds as follows:

- Power up T-Scan ED (see Starting a T-Scan ED exam, page 3-1).
- Log into the system (see, page 3-2).
- Enter patient information in the Patient List screen (see Description of Patient List Screen, page 4-2).
- Enter clinical breast examination result (CBE is a prerequisite of the T-Scan™ exam).
- Position the patient for examination (see Positioning the Patient for the Examination, page 4-7).
- Apply gel to the signal transmitter and place it in the patient's hand contralateral to the examined breast. Ask the patient to hold it tightly.
- Apply conductive gel to the surface probe and/or the breast to be examined.
- Perform the examination (see Conducting an Examination, page 4-8).

Starting a New Examination

Start an examination by entering patient information on the Patient List screen. This can be done for new patients or returning patients.

Description of Patient List Screen

The Patient List screen is the first screen that appears after login. This screen may also be accessed by pressing the Patient List icon  from the Examination screen. The Patient List screen (see below) is divided into an upper and lower half. Use the upper half of the screen to enter a new patient or to search for the record of a previously examined patient. The lower half of the screen contains a list of all the patients that have been examined.

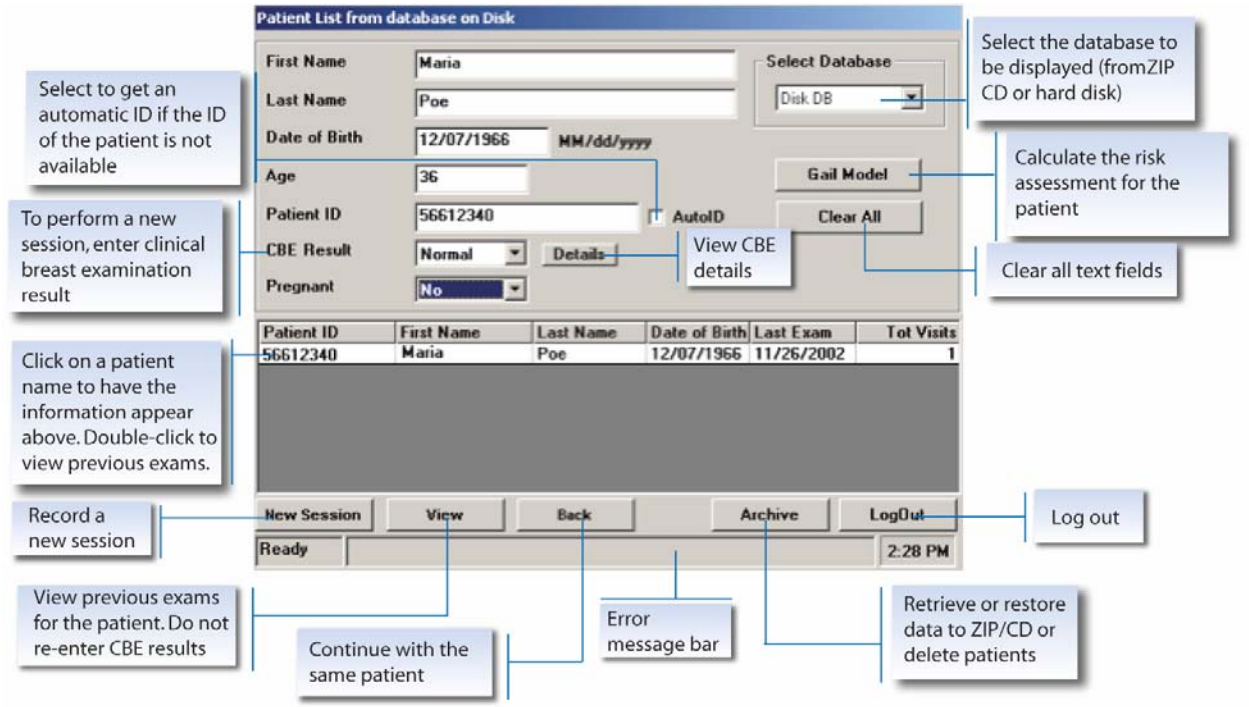


Figure 12: The Patient List screen

Entering a New Patient Record

All fields of the **Patient List** screen must be completed before proceeding with a T-Scan ED exam.

To enter a new patient record

1 Open the **Patient List** screen.

2 Complete the following fields in the **Patient List** screen to enter a new patient:

- Last name
- First name
- Date of birth (MM/DD/YYYY)
- Age
- ID number. If the ID number is not available for the patient, click in the AutoID box to generate an automatic and unique ID number. Do not try to type an ID number if AutoID is selected.

> Note: It is strongly recommended to use the Auto ID feature

- Result of the clinical breast examination (CBE) (Normal or Abnormal). To enter details about the CBE result, press Details and enter information in the relevant fields.

  (see **Figure 13**: **CBE Details** dialog box).
- Pregnancy status (Yes or No). No scanning is allowed for pregnant women.
- If "Yes" is selected, the following message will be displayed: "Note. The T-Scan™ exam is contraindicated in pregnant patients".
- Optionally, calculate the Gail Model Risk Assessment for the patient. To enter,
- Press Gail Model (see Figure 14: Gail Model dialog box).
- The relevant fields are enabled as the information is filled in. When all the information has been entered, press **Preview**. The lower part of the screen will show the result of the calculation with estimates for a 5-year risk and lifetime risk. To save in database and exit, press **OK**. To exit without saving, press **Cancel**.

> Note: T-Scan ED should always be used in conjunction with CBE and not as a stand-alone procedure.
>
> T-Scan ED examinations are not performed during pregnancy. If the Pregnant box is marked YES, the system will not allow scanning.

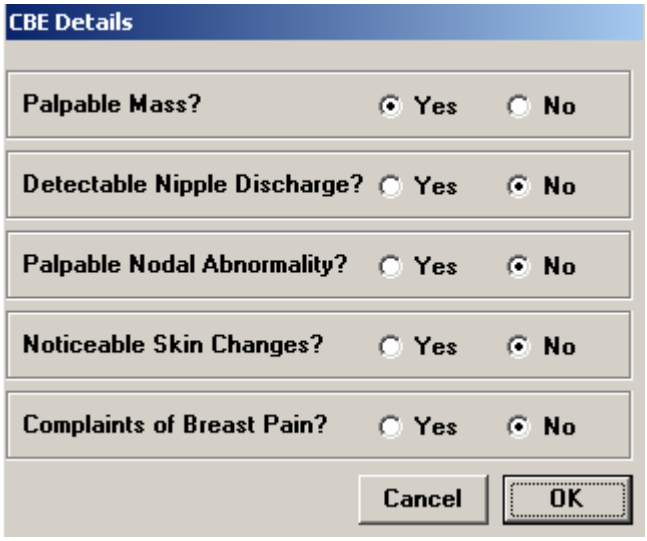


Figure 13: CBE Details dialog box

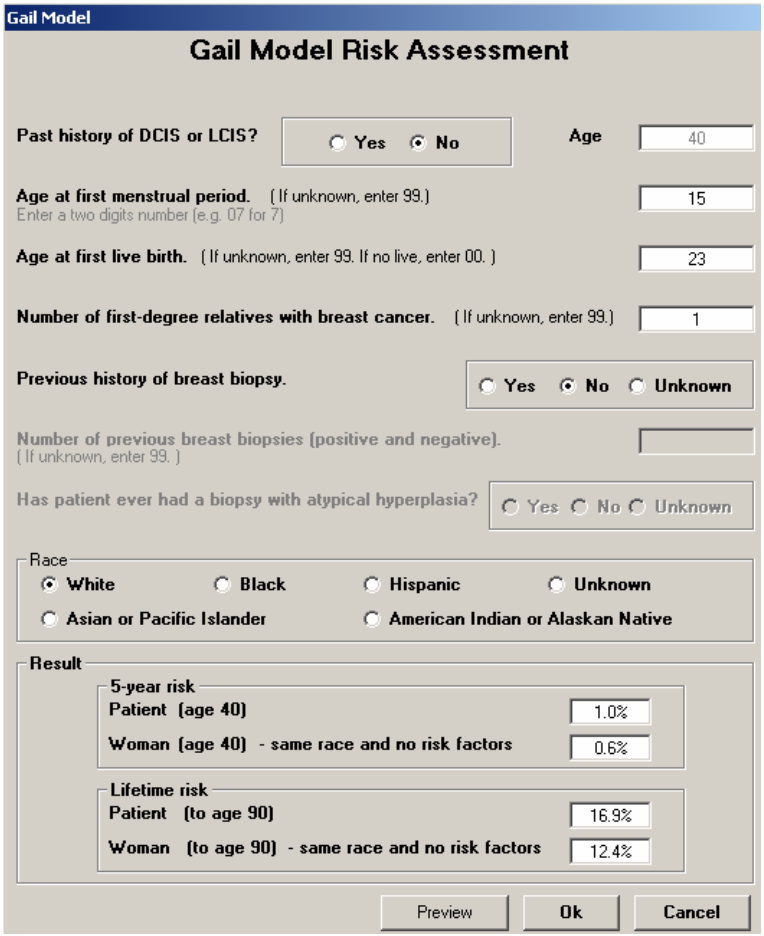


Figure 14: Gail Model Risk Assessment dialog box

Note: The printout of the report for the Gail Scale calculation is only possible *after the scan has been completed*.

Entering a Record for an Existing Patient

T-Scan ED stores all patient exam information in a database file. You can easily retrieve patient records when a patient returns for another examination. You may retrieve records of previous exams by either patient name or ID number.

To find and display a patient record

1. Enter the First Name, Last Name or ID Number of the patient who has existing exams in the appropriate fields in the upper half of the Patient List screen; a short list of patients corresponding to the entered data appears on the bottom half of the screen.
2. Click on the patient; the information for that patient appears in the upper half of the screen.

OR

1. Scroll through the **Patient List** until the name of the desired patient appears.
2. Click on it to have the details appear in the upper half of the screen.

OR

1. Click on the button of one of the four criteria (Patient ID, First Name, Last Name or Date of Birth) to sort the list as needed.
2. Click on the desired patient; the information for that patient appears in the upper half of the screen.

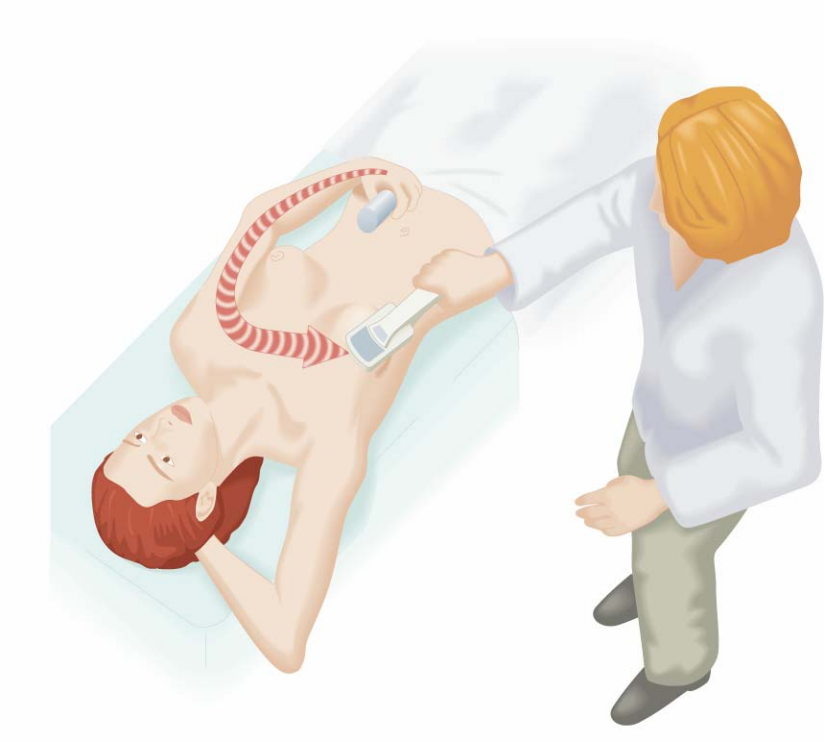
Opening the Examination Screen

After you have entered patient information on the **Patient List** screen, you are ready to open the **Examination** screen.

To open the Examination screen

1. Enter the result of the current clinical breast examination and the pregnancy status (obligatory before each new examination).
2. Click on the 

button to perform a new examination.



Positioning the Patient for the Examination

Before actually starting the recording, ask the patient to lie on her back on the bed. Position her as in the photo, so that she is comfortable and can easily hold the signal transmitter. The orientation of the patient depends on the breast to be examined. If the right breast is to be examined, position her with a pillow under her right shoulder and ask to place her right hand above her head. Thus, the right breast is presented more or less vertically for optimal examination exposure. When examining the left breast, transfer the pillow to the left shoulder, and rotate the patient to her right side.

Signal transmitter and Surface probe

The signal transmitter that generates the electrical signal is held in the patient's hand contralateral to the examined breast. Thus, when examining the right breast, the signal transmitter is held in the left hand and vice versa.

> ☝ Note: Some patients may feel a slight tingling in the hand as a result of the current in the signal transmitter. This is not dangerous to the patient.

Ultrasound gel or water based massage gel is used during a T-Scan exam in order to help ensure better contact between the breast and probe, and also to make the exam more comfortable for the patient and the physician by decreasing friction as the probe is moved from one sector to another. We recommend a low-viscosity, water based gel (*e.g.,*

Pharmaceuticals Innovations' Gamma Gel) because such gels tend to trap less air bubbles and thus avoid artifacts. Furthermore, low viscosity, water based gels are easier to remove from both the patient and the probe once the exam is completed. Apply a thin layer of gel on the signal transmitter and on the surface of the probe.

Conducting an Examination

After you have finished the physical preparations for the examination, you are now ready to start the examination. The examination is carried out using the **Examination** screen.

The Examination Screen

The **Examination** Screen allows a complete recording of both breasts (nine sectors each). The nine sectors are arranged in a 3 x 3 grid with the nipple sector in the center.

To view previous exams, use the arrows provided at the bottom of the grid.

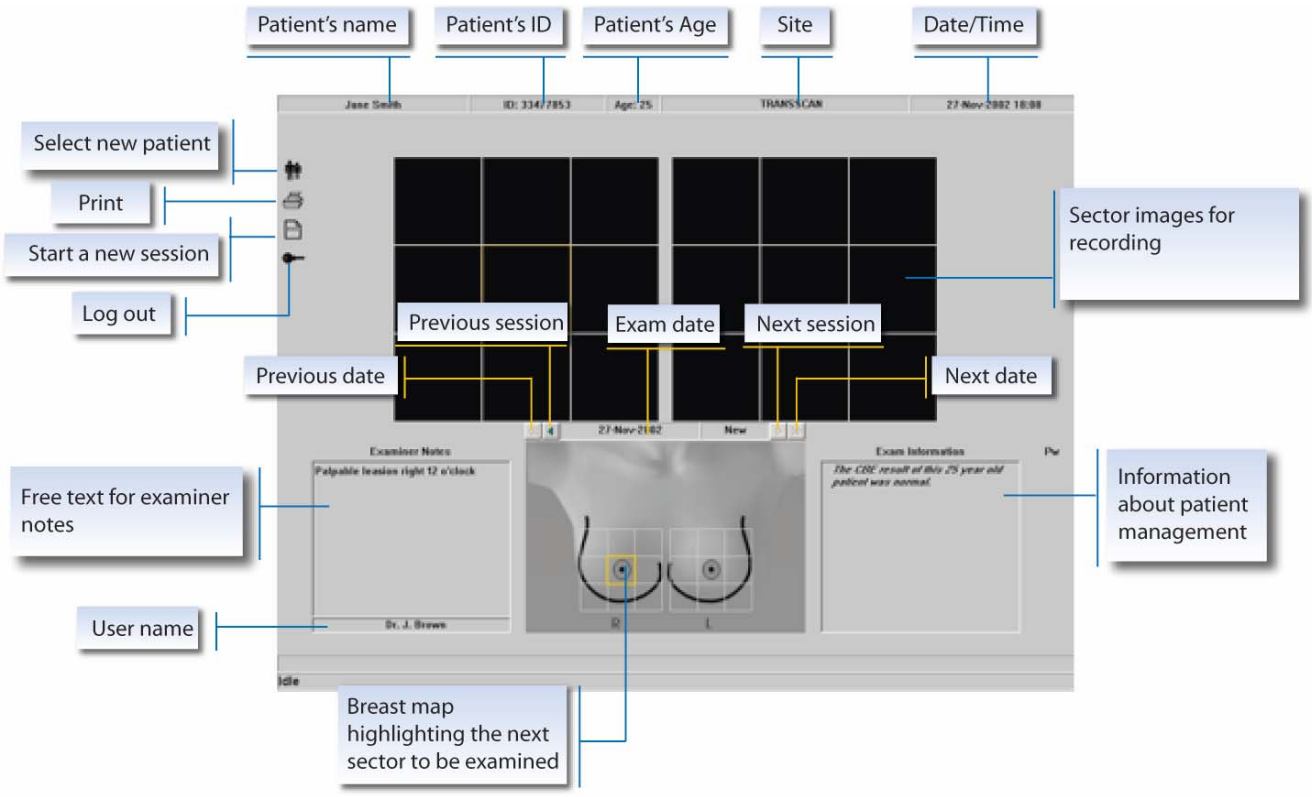
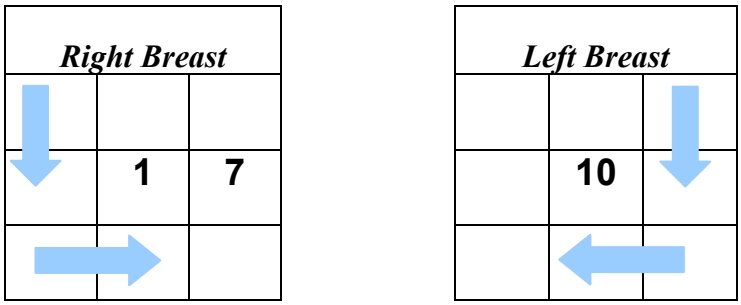


Figure 15: The Examination screen

Making a Recording

ORDER OF RECORDING

Recording begins with the nipple of the right breast and continues to the Right Upper Outer Quadrant *anti-clockwise,* following the sequence shown below for the right breast and indicated as a yellow outline on the corresponding sector on the screen. After switching the electrode from the patient's left to right hand, continue from the left nipple *clockwise* following the sequence shown below and indicated by a yellow outline on the corresponding sector on the screen.



T-Scan ED does not identify wrong positioning on the breast. For optimal breast coverage, it is important to place the surface probe in the sector that corresponds to the breast (*e.g.,* sector 7 is located at 3 o'clock).

RECORDING TECHNIQUES

Note: While recording, take care to avoid recording over bones such as the ribs or the clavicle; bones will appear as white objects in the image, providing misleading information. This is especially relevant to small breasts.

It may be necessary to reapply gel to the surface probe / breast several times during the course of the examination.

If the examiner is standing on the left side of the patient, the surface probe should be oriented with the handle protruding toward the Examiner's left as follows:

Figure 16: The Surface probe Orientation

To make a recording

- Place a ring of gel around the nipple and on the surface probe. Position the patient so that the nipple is pointed directly upright.
- While holding the surface probe, click the **START/STOP** button  on the surface probe. The **START/STOP** indicator on the surface probe is lit. The T-Scan ED image appears in real time on the monitor, so that the surface probe can be best positioned before starting to record.
- Press the surface probe onto the nipple, starting deliberately off center (laterally). Slide the surface probe into position, so that the nipple (detected as a bright area on the screen) is in the center of the surface probe. Try to obtain a solid nipple rather than a ring nipple (see **Figure 17**: **Nipple Pattern Recordings**).

> Note: A solid nipple recording will ensure optimal diagnostic characteristics. This is not always attainable in the first instance. It may be necessary to request the woman to lie slightly laterally in order to achieve this result. In this case, bring in the surface probe from the lateral aspect of the nipple.

Solid nipple: **Ring nipple (not optimal):**

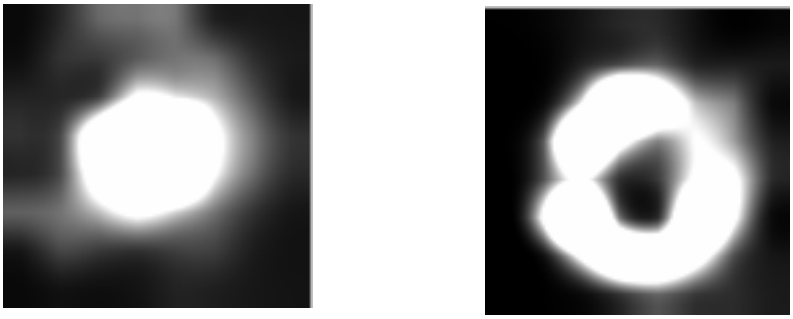


Figure 17: Nipple Pattern Recordings

> Note: Trapped air bubbles near the nipple appear as black spots in the image. To remove the bubbles, apply gel to the nipple and reposition the surface probe or move the surface probe slightly until bubbles disappear.

1 The system will prompt the user regarding optimal skin contact /stability of recording by means of a green vertical gauge. As soon as the surface probe contact is stable, the message **Ready to record** will appear in the sector being recorded, and it will be circumscribed by a green line (see **Figure 18: The Green Gauge**). Hold the surface probe steady until the bar rises to the highest stable position and then select REC on the surface probe. The REC indicator on the surface probe is lit. Recording begins.

> Note: To help ensure best quality recording, error messages are generated by the system (see Appendix B: Error Messages).
>
> Complete steadiness is essential in order to ensure proper multiple-frames recording.

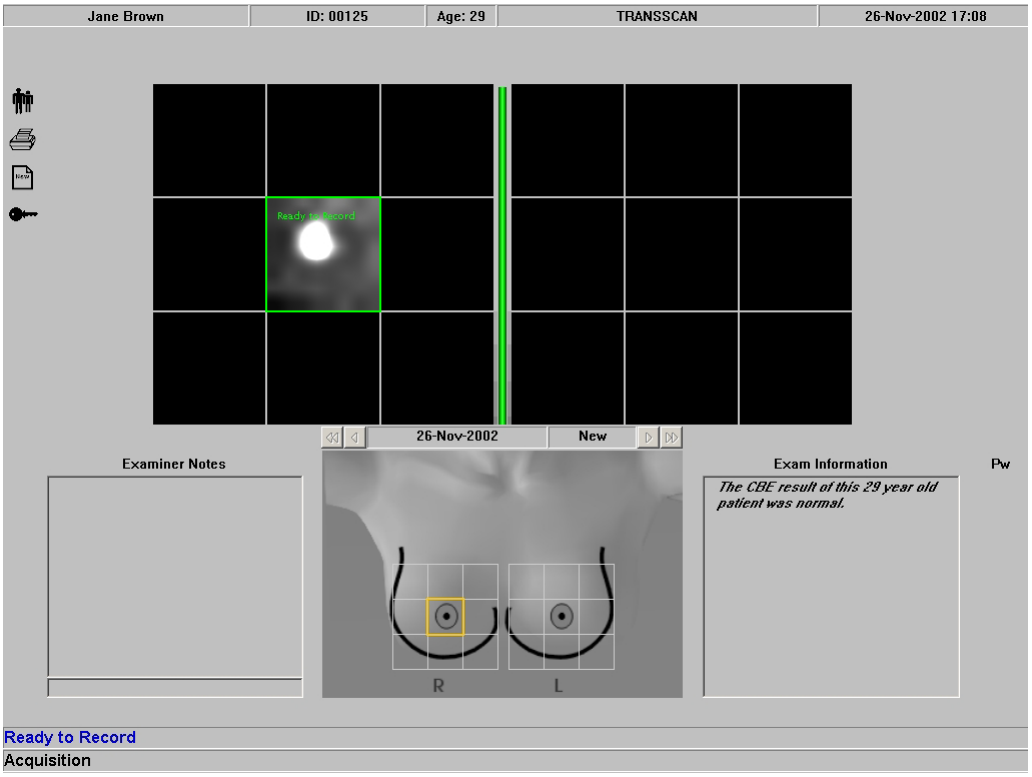


Figure 18: The Green Gauge indicating optimal contact.

2 The end of recording is indicated by a soft beep. At the end of recording, both **START/STOP** and the **REC** indicators are turned off.

3 If the recording was successful, no error message is displayed and the next sector to record is highlighted on the screen. If the recording was not successful, an error

message is displayed (see **Figure 19A: Recording not successful message**). In some cases, the faulty frame is shown (see **Figure 19B: Recording Error** screen). Record again after pressing the **Record again** button or **Yes**. If the error message persists after several attempts, skip rerecording by choosing **Ignore** or **No**. The faulty sector will be marked by a blue frame at the end of recording and the message **Insufficient data on marked sectors** will appear. In some instances, the diagnostic interpretation may not be provided.

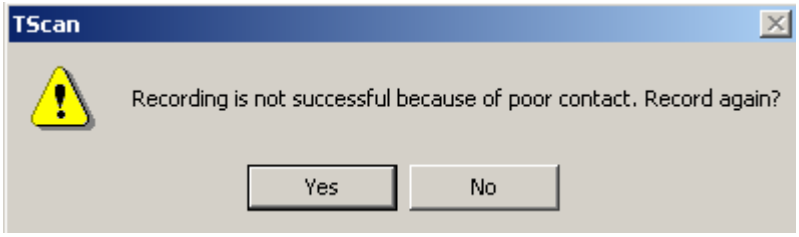


Figure 19A: Recording not successful message

Figure 19B: Recording Error screen

4 On non-nipple sectors, good contact is achieved when the sector image displays smooth shades of gray (see **Figure 20: Example of Recorded Images**). Try to avoid air bubbles (seen as black spots on the screen), white edges or white/black corners. Screen messages aim to guide the user to better surface probe/skin contact. Check patient's grip on signal transmitter or add gel on electrode and surface probe or reposition the surface probe if necessary.

5 Move the surface probe to the next highlighted sector and repeat steps 2-7. Continue until recordings are completed from all sectors on the right breast. The nipple sector on the image of the left breast will then be highlighted.

6 Repeat steps 1-5 for the left breast.

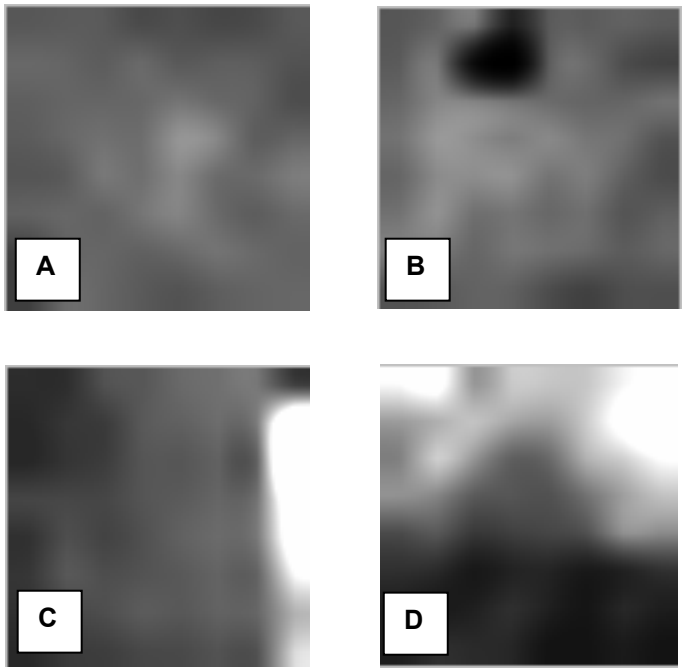


Figure 20: Example of good (A) and bad (B, C, D) recorded images (A: proper image of consistent gray, B: image with air bubble appearing as black spot, C: image with white edge, D: image with white/black corners)

Note: It is recommended that when recording from a sector other than the nipple, you place the surface probe along a line extending from the nipple to the sector. Start at a position on that line peripheral to the breast. From this point, press the surface probe against the breast, and slide it along that axis toward the nipple until the surface probe is in the desired position. In this manner, breast tissue is pressed toward the nipple, and any bubbles or areas of poor contact are removed during the pressing. When recording from the lower sectors, the best contact of the surface probe is maintained by using a scooping motion to push the surface probe toward the sector.

To repeat a sector recording

1 Click on the image of the sector where rerecording is needed (sector marked with blue frame). The sector is highlighted.

2 Record that sector again.

Final Exam Result

At the end of a breast scan, the overall EIS status of the woman is indicated as a line at the bottom of the image. A green line, which is solid, indicates that EIS measurements of the breast are within a normal range. A red hatched line indicates that further investigation is recommended with other modalities (ultrasound, mammography).

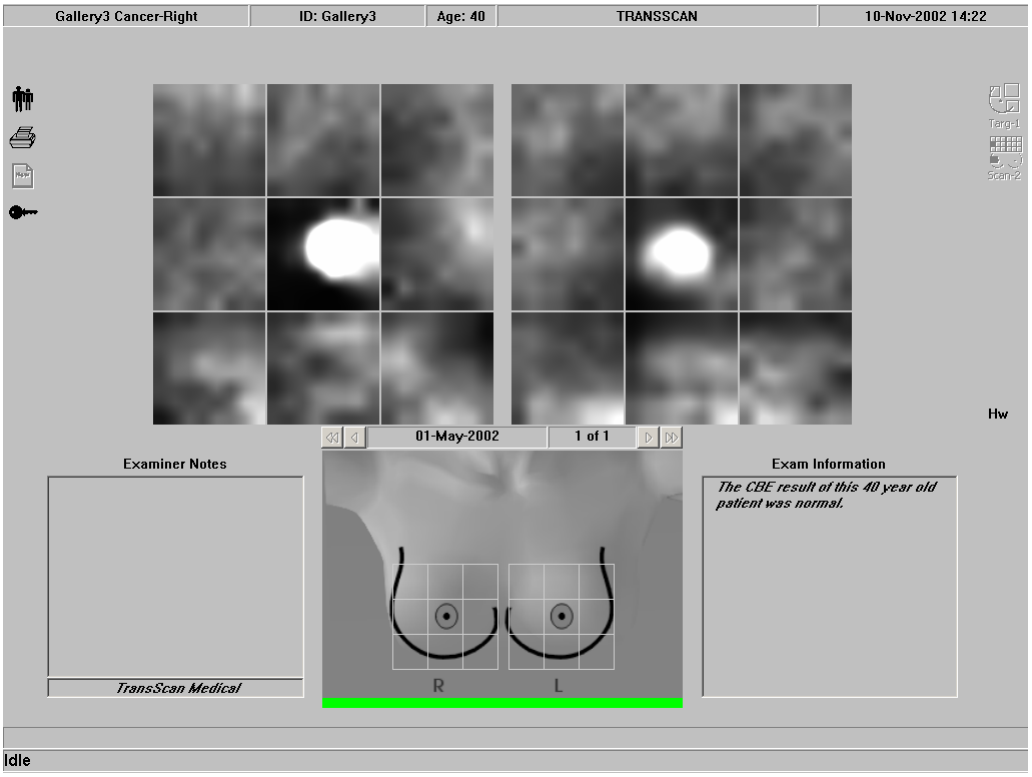


Figure 21: Diagnostic Interpretation

Printing

Use the printing function (if printer is connected) to print clinical data. To print, click the **Print** icon on the screen (if enabled). The report includes a printout of the patient information, the T-Scan result and a Gail Model Risk Assessment.

Starting a New Session

Recordings are classified by date and session. A session refers to the images from a given examination. **Date** contains all the images acquired on a specific date. Use the **Previous Date** and **Session** and **Next Date** and **Session** buttons to move back and forth between dates and sessions.

To start a new session with the same patient

Press the  icon on the **Scan** screen; the previous results on the screen are cleared.

To start a new examination for an additional patient

After finishing an exam for a patient, press the **Patient List**  button to start an exam for a new patient.

Ending the Examination

! CAUTION: After each examination, always thoroughly clean the T-Scan ED surface probe with 96% alcohol to remove residual gel or body fluids. Failure to do so can result in the surface probe producing inaccurate recordings.

Cleaning and Disinfecting

1. Using a lint-free cloth or paper towel, remove the gel from the surface probe and signal transmitter.
2. Wipe with a clean cloth soaked in 96% alcohol.
3. Visually inspect the surface probe and electrode to ensure cleanliness.
4. Air dry the surface probe and signal transmitter for a few minutes.

WARNING!

Failure to DISINFECT the surface probe may result in transfer of contaminants between patients.

Chapter 5

Managing the Database

This chapter covers how to:

- Backup patient records on a ZIP or CD.
- Find and review patient records.
- Restore patient records.
- Delete patient records.

Archiving Patient Records

As examinations accumulate, you may want to store them on a ZIP or CD. This is done using the Archive screen.

The Archive Screen

Use the Archive screen to:

- Backup patient records on ZIP or CD.
- Restore patient records from ZIP or CD
- Delete patient records from hard disk.

To open the Archive Screen

- From the Patient List screen, select the **Archive** button.

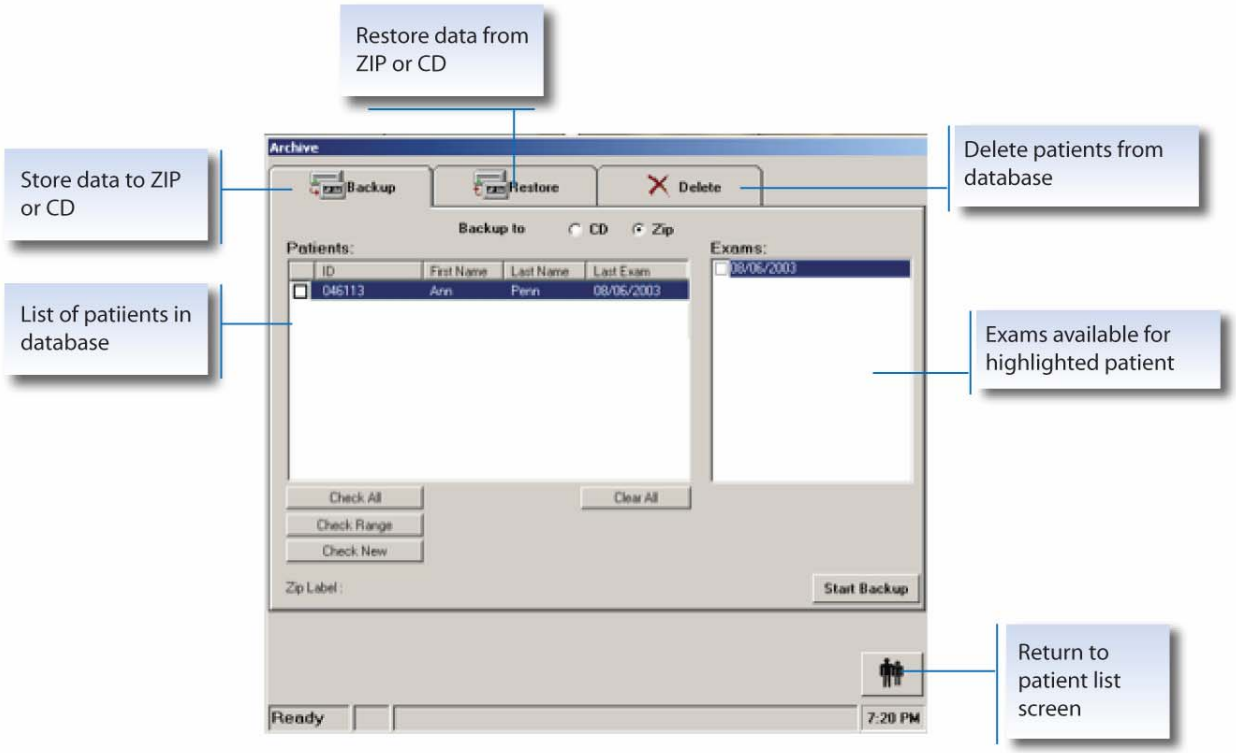


Figure 22: The Archive screen

Backing up Patient Records

It is recommended to regularly backup patient records from the hard disk database to a storage medium such as ZIP disk or CD.

To backup a patient record

1. Select **Backup** (this is the default tab that appears when you press the **Archive** button). Check **ZIP** or **CD radio** button.
2. In the list of patients (left part of the screen), select the patients to backup. For each selected patient, select the exams to backup (right part of the screen). By default, all the patient's exams will be selected. Use **Check All** to store all the patients/exams available in the database. To store a short consecutive list of patients, check the first and last patients of the short list and use **Check Range**. To store new patients only, use **Check New**.
3. Press **Start Backup** button.
4. Wait until the message **Backup is completed successfully** appears and the disk is ejected.

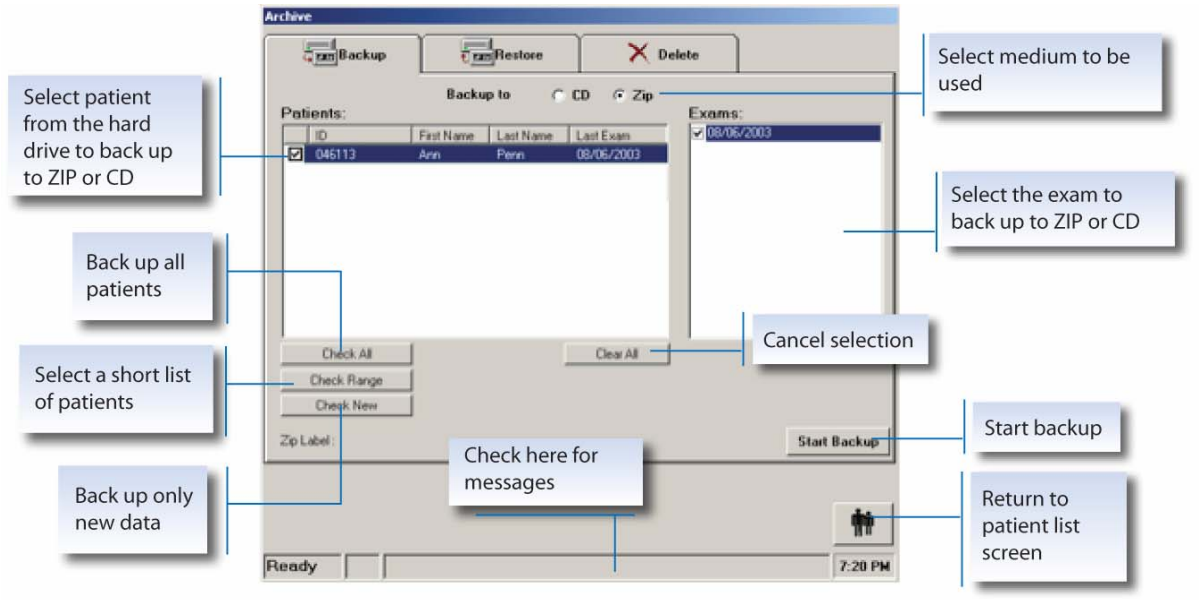


Figure 23: Backing up data

5 If there is not enough space available on the disk or if the drive is not ready, messages are generated by the system. Replace the disk if necessary and follow the instructions. At the end of the backup procedure, wait for disk to be ejected as indicated.

Restoring Patient Records

It is possible to restore data from the storage space (ZIP disk or CD) to the hard disk.

To restore patient records

1 Select **Restore** from the **Archive** screen. Check **ZIP** or **CD radio** button.

2 In the list of patients (left part of the screen), select the patients to restore. For each selected patient, select the exams to restore (right part of the screen). By default, all the patient's exams will be selected. Use **Check All** to restore all the patients/exams available in the storage database. To restore a short consecutive list of patients, check the first and last patients of the short list and use **Check Range**. To restore new patients only, use **Check New**.

3 Press **Start Restore** button.

4 Wait until the message **Restore is completed successfully** appears.

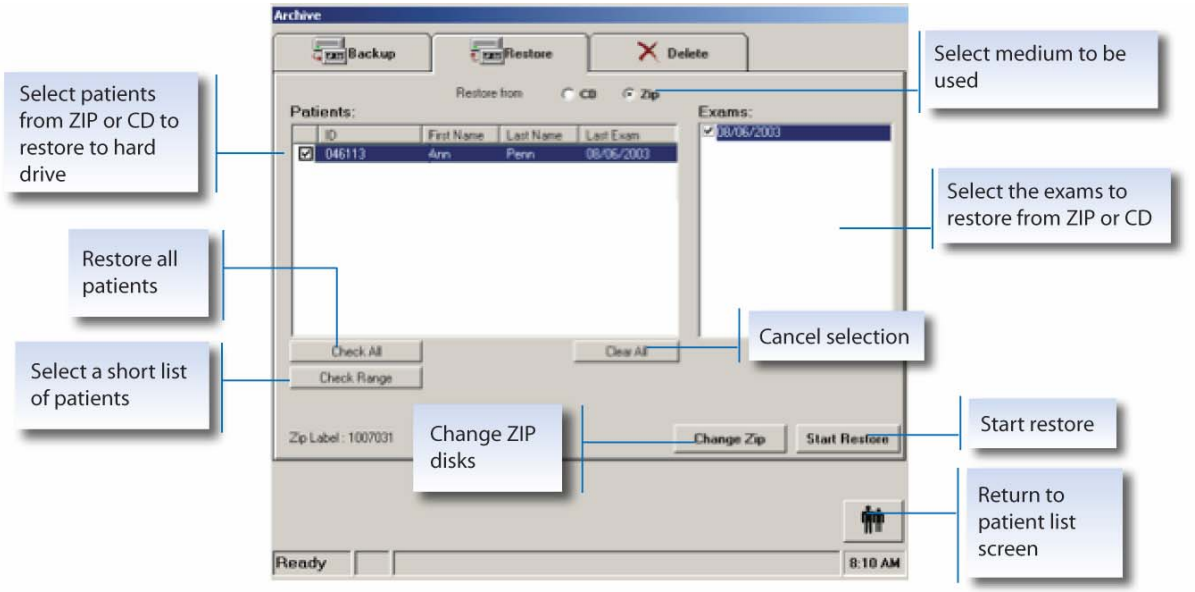


Figure 24: Restoring Data

Deleting Patient Records

> Note: Before deleting data, be sure it is saved in an alternate storage place.

It is possible to delete data from the hard disk database.

To delete a record

1. Select the **Delete** tab from the **Archive** screen.
2. In the list of patients, select the patients to delete. Use **Check All** to delete all the patients/exams available in the database. To delete a short consecutive list of patients, check the first and last patients of the short list and use **Check Range**.
3. Press **Delete Patient** button.
4. Confirm delete by selecting **Yes**.
5. Wait until delete is finished.

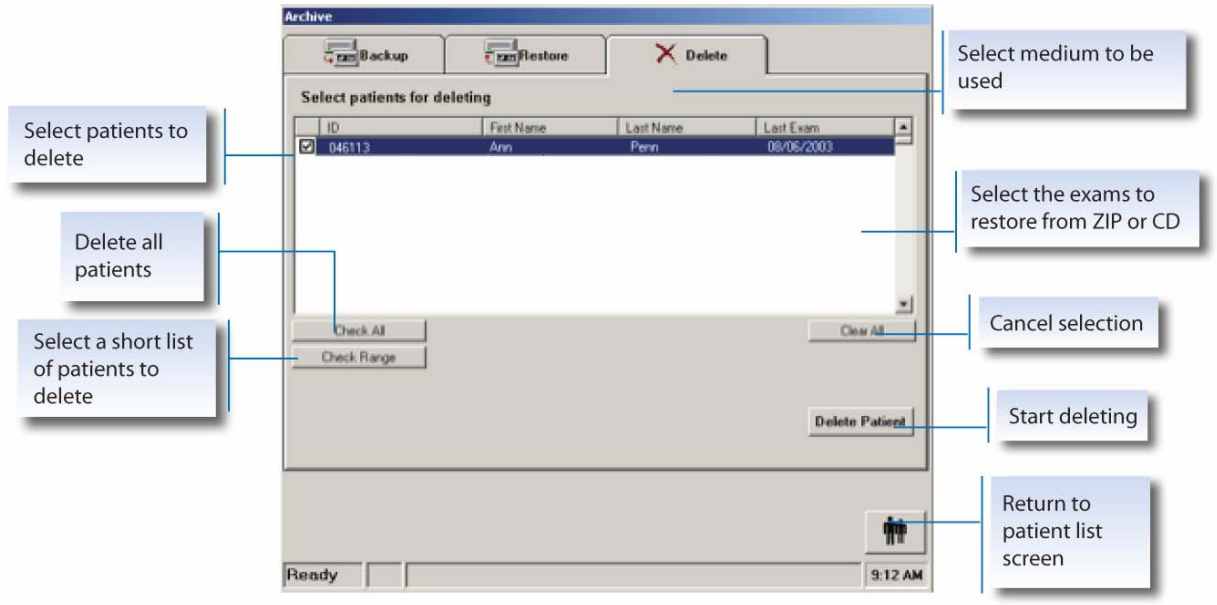


Figure 25: Deleting Records

Finding and Reviewing Patient Records

To review previous examinations for a patient

- Click on the **View** button to review previous exams for this patient.

To locate a patient record in a ZIP disk or a CD

- Select the ZIP or CD database in the **Patient List** screen (see **Figure 12: The Patient List screen**); the list of patients stored in the ZIP or CD appears. This database is read-only.

Chapter 6
Appendices

Appendix A: Troubleshooting

Note: In the event of a power failure (or when the machine is disconnected from the power socket), a beeping sound will be heard and the message "Utility failure" will appear on the screen on a background of clocks. If the system is reconnected to the power source, the beeping noise will cease and the user can shut down the error screen. If not, the user may continue working for 5 minutes until there is an automatic system shutdown. The message, "It is now safe to turn off your computer" will appear and the **ON/OFF** button should be pressed.

Symptom	***Likely Cause***	***Solution***
Acquisition error.	Hardware problem.	Reboot the system and attempt acquisition again. If problem persists, call service representative.
Acquisition stopped due to Overcurrent.	User may have inadvertently made contact between signal transmitter and surface probe.	Ensure correct handling of surface probe and electrode.
Acquisition stopped due to Overflow.		Clean surface probe and ensure stable contact representative.
Can not archive cases to CD.	CD drive is not ready or CD is full.	Check CD drive or replace CD if it is full.
Cannot archive cases to ZIP disk.	ZIP disk not properly placed in ZIP drive, ZIP drive not properly connected or ZIP disk is full.	Check placement of ZIP disk or check connection of ZIP drive or replace ZIP if it is full.
Can not read Hardware Parameters from registry.	Corrupted registry.	Call service representative.
Cannot read Working Mode from Registry. Please reinstall the program.	Corrupted registry.	Call service representative.

Symptom	*Likely Cause*	*Solution*
Dark spot in a specific sector that changes location when moving the surface probe.	Air bubble.	Apply more gel to surface probe and slightly move the surface probe.
Dark spot in the same region of each sector image.	Surface probe dirty or sensor defective.	Clean the surface probe with alcohol 96%. If problem persists, call service representative.
Error reading Working Mode from file.	Some files were mistakenly deleted.	Call service representative.
Failure in all comparators.	Hardware problem.	Call service representative.
Failure in the first comparator.	Hardware problem.	Call service representative.
Failure in the second comparator.	Hardware problem.	Call service representative.
Failure in the third comparator.	Hardware problem.	Call service representative.
Front End Initialization Error.	Hardware problem.	Reboot the system. If problem persists, call service representative.
Hardware error. Please restart the system. If error persists, call service representative.		Call service representative.
Overcurrent test failed. Acquisition is not allowed.	Hardware error prior to acquisition.	Call service representative.
Picture uniformly too dark.	No contact or improper settings for brightness and contrast.	Ensure better contact. If problem persists, return settings to factory default levels (default gray level icon).
Picture uniformly too light.	Improper settings for brightness and contrast.	Return settings to factory default levels (default gray level icon).
Surface probe does not slide smoothly over the skin.	Not enough gel.	Apply more gel.
There is only X GB Free on the % c drive! Further acquisition is disabled. Free some space on this drive.	Hard disk is full.	Clean temporary file – Empty recycle bin, etc., or call service representative.
Unable to print.	Printer not turned on or needs paper or is malfunctioning.	Ensure printer is turned on or replace paper or check for error message in printer message window.
White areas in the corners of sectors	Poor contact between the surface probe and the breast surface.	Apply more pressure when recording.

Appendix B: Error Messages

Note: Always check error messages at left lower side of screen if the procedure stalls.

Error Message	***Likely Cause***	***Solution***
Cannot make changes. The DataBase is Read Only.	If DB is Read Only then changes are not allowed by design, in order to preserve original user intention.	Change DB from CD DB to Disk DB. By design the CD DB is not writable.
Contact is not sufficient. Please, ensure better contact.	Not all segments of the surface probe are in good contact with the breast or insufficient gel applied to surface probe.	Add gel and reposition the surface probe.
Insufficient data on marked sectors.	Recording of some sectors was not successful. These sectors are highlighted in blue.	Record these sectors again.
No contact.	No contact was initiated.	Ensure contact of surface probe on breast.
No default printer available.	Printer not installed or not connected.	Ensure printer connection.
Not ready to record.	Record button was activated during acquisition before contact was sufficient.	Ensure contact. Then press Record.
Partial contact.	Check for possible air bubble.	Ensure contact of surface probe on breast.
Please, call service representative.	Instrument is not functioning properly.	Seek help from a service representative.
Please, check signal transmitter and surface probe positioning.	Signal transmitter is not held tightly enough or does not have enough gel.	Apply more gel to signal transmitter and make sure that the patient holds it tightly.
Please, position the nipple in the center of the sector.	Nipple is not in the center of the image.	Center the white spot of the nipple in the designated segment.
Poor contact.	The patient may not be holding the signal transmitter correctly or surface probe contact is not optimal.	Check patient grip on signal transmitter. If this does not solve the problem, then try to improve position of surface probe.
Recording is not successful because of insufficient stability. Record again?	The recording of multiple frames was not steady.	Press **Record Again** if you wish to rerecord. If you press **Ignore**, you may not get a diagnostic result.

Error Message	*Likely Cause*	*Solution*
Recording is not successful because of partial contact. Record again?	The surface probe may have moved during the recording process or it was lifted before recording was complete.	Press **Record Again** if you wish to rerecord. If you press **Ignore**, you may not get a diagnostic result.
Recording is not successful because of poor contact. Record again?	The surface probe was not in proper contact during the recording process.	Press **Record Again** if you wish to rerecord. If you press **Ignore**, you may not get a diagnostic result.
Recording of nipple is not successful. Record again?	The surface probe was not in proper contact with the nipple during the recording process.	Press **Record Again** if you wish to rerecord. If you press **Ignore**, you may not get a diagnostic result.
Session is locked.	Changes are not allowed after the user has exited an exam.	Do not exit to patient list if you still wish to make changes, *e.g.,* insert text or rerecord.
The algorithm is not available because of insufficient data.	Recording of some sectors was not successful. These sectors are highlighted in blue.	Record these sectors again to get algorithm result.
Values out of range. Try to reposition the surface probe.	The surface probe collects out of range signals from the system.	Reposition the surface probe and record again.

Appendix C: Technical Data

Nominal Voltage/Nominal Frequency

115V / 230V ± 10% 50Hz / 60Hz

Nominal Connection Current

1.5A@230V, 3A@115V corresponds to the rated value of the fuse in the main input of the product.

Maximum Power Consumption

1.2 KVA

INPUT POWER VALUES:

System Voltage	Frequency	Nominal Input Power Rating
115V	50/60Hz	80VA
230V	50/60Hz	80VA

WARNING!

For the main power supply connection, use only parallel blade grounding type hospital grade attachment plug.

Grounding reliability can only be achieved when the equipment is connected to an equivalent receptacle marked “hospital grade”.

Internal Replaceable Power Sources

The system contains two replaceable power sources:

- A battery in the Uninterrupted Power Supply (UPS, optional) and
- A battery in the mother board of the computer.

Both these batteries are not user-serviceable, and should be replaced only by an authorized Mirabel Medical Systems representative.

Printer (optional)

A printer can be connected to the system via USB isolated channel.

Environmental Conditions

OPERATION

Temperature Range: + 10^0C to +40^0C
Relative Humidity: 15% to 75%, non-condensing
Atmospheric Pressure range 700hPa to 1060hPa

WARNING!

The system is not sealed against ingress of liquids. Clean the system with a damp cloth only.

STORAGE AND TRANSPORTATION

Temperature Range: -40^0C to +70^0C, according to IEC 60721-3-2
Relative Humidity: 15% to 93% non-condensing

Protection Against Electric Shock

WARNING!

The system is optionally equipped with a Universal Power Supply (UPS), that activates automatically in case of power failure or when the system is disconnected from the Mains without being shutdown. Therefore, dangerous voltage may be present in the system even when the system is disconnected from the Mains.

PROTECTION CLASS

Class I, according to IEC 601-1;
Degree of protection type BF according to IEC 601-1.

RADIO INTERFERENCE SUPPRESSION

FCC Part 15 Subpart A
IEC 601-1-2 (9/94) product group 1, limit class B, CISPR 11

Flammability Class

Not suitable for use in the presence of flammable mixtures.

System Output

Max Voltage 2.5V.
Diagnostic Current less than 5mA.
Applied frequency with respect to IEC 601-1-2.

Clinical Protocol

Panel Pack Pages 213-249 Redacted

Post Approval Study (Proposed)

Panel Pack Pages 250-252 Redacted

Peer Reviewed Publications

Panel Pack Pages 253-278 Redacted Due to Copyright Issues

Redacted Articles:

Stojadinovic A, Moskovitz O, Gallimidi Z, Fields S, Brooks AD, Brem R, Mucciola RN, Singh M, Maniscalco-Theberge M, Rockette HE, Gur D, Shriver CD Prospective study of electrical impedance scanning for identifying young women at risk for breast cancer. Breast Cancer Res Treat 97:179-89. 2006.

Pisano ED, Gatsonis C, Hendrick E, Yaffe M, Baum JK, Acharyya S, Conant EF, Fajardo LL, Bassett LW, D'Orsi C, Jong R, Rebner M. Diagnostic performance of digital vs film mammography for breast cancer screening. NEJM 353:1773-83. 2005.

Smith-Bindman R, Chu P, Miglioretti DL, Quale C, Rosenberg RD, Gary C, Geller B, Bacchetti P, Sickles E, Kerlikowske K . Physician predictors of mammographic accuracy. J Nat Cancer Inst 97: 358-67. 2005.

Banks E, Reeves G, Beral V, Bull D, Crossley B, Simmonds M, Hilton E, Bailey S, Barrett N, Briers P, English R, Jackson A, Kutt E, Lavelle J, Rockall L, Wallis, MG, Wilson M, Patnick J. Influence of personal characteristics of individual women on sensitivity and specificity of mammography in the Million Women Study: cohort study. BMJ 329:477. 2004.

Poplack SP, Tosteson AN, Grove MR, Wells WA, Carney PA. Mammography in 53,803 women from the New Hampshire mammography network. Radiology 217: 832-40. 2000.

Duffy SW, Chen HH, Tabar L, Fagerber G, Paci E. Sojourn time, sensitivity and positive predictive value of mammography screening for breast cancer in women aged 40-49. Int J Epidemiol 25:1139-45. 1996.

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Michael J. Pencina, PhD

Below please find our analysis of two questions relating to the efficacy of the T-Scan device compared to both the standard of care for women age 40-50, and to the rate of cancer detection in a random selection of patients in the target population of women 30-40 years of age.

1. The T-Scan is intended to identify young women who should consider a mammogram earlier than the typical initiation of screening mammography at age 40. In order to demonstrate the clinical utility of the T-Scan device, compare the absolute rate of breast cancer in women age 30-40 who are positive on T-Scan compared to the absolute rate of breast cancer in women age 40-50 who are routinely offered mammography.

Based on published studies conducted on random samples of women age 40-49 (see table below), we estimate the cancer detection rate at 117/49508 = 0.0024 or 1 cancer in 423 women screened (Exact 95% confidence limits around this rate are 0.0020 to 0.0028).

# Women Screened	# Cancers Detected	Yield (Cancers/Mammogram)	Reference
35,896	83	1:432	Bjurstam *et al.*, 1997.
4,744	8	1:593	Burhenne *et al.*, 1991
8,868	26	1:341	Kerlikowske *et al.*, 1993
49,508	**117**	**1:423**	Totals

The reported Sensitivity and Specificity of T-Scan are 26.4% and 94.7%, respectively. Of interest, the 95% (exact) confidence interval around the Sensitivity rate is 17.6% to 37.0%.

Also, it can be assumed (Kerlikowskė *et al.*, 1993) that the cancer rate in women 30-39 years of age is approximately 15 per 10,000. For simplicity of presentation, let us assume that we have 10,000 women of 30-39 years of age. 15 of them have breast cancer and 9985 do not. Of the 9985 cancer-free women, T-Scan with a Specificity of 94.7 will classify about 9456 (=9985*0.947) women as low risk and the remaining 529 as high risk, or "T-Scan Positive" (9985-9456). Out of the 15 women with cancer, T-Scan with 26.4% Sensitivity will classify about 4 women as high risk and about 11 as low risk.

The above discussion can be summarized in the table below:

Cancer Diagnosis	High Risk	Low Risk	Total
Yes	4	11	15
No	529	9,456	9,985
Totals	533	9,467	10,000

Hence, T-Scan classifies 533 women as high risk, 4 of whom actually have cancer. This gives a detection rate of 4/533 = 0.0075 or 1 in 133 women. Reasoning in an analogous fashion with the lower Sensitivity limit (17.6%), we obtain 2.6/531.8 = 0.0049 or 1 in 205 as the detection rate. Using the upper Sensitivity limit (37.0%), we get 5.5/534.7 = 0.0103 or 1 in 97 women.

Hence, the T-Scan detection rate can be estimated as 0.0075 with a 95% confidence interval of 0.0049 to 0.0103, which is significantly above the detection fraction for women 40-49 years of age (0.0024) and its confidence interval (0.0020 to 0.0028).

We note that the choice of the 10,000 was made for the simplicity of illustration and that the same result is obtained with any other number.

2. The T-Scan is designed to identify approximately 5% of the population of younger women which is at increased risk for breast cancer. What is the cancer rate in the T-Scan positive "at risk" cohort when compared to a randomly selected cohort of the same size?

Based on the 2004 US Census, 14.1% of 145,908,683 or 20,573,124 women are between 30 to 39 years of age. 0.15% of them suffer from breast cancer.

For simplicity, assume a population of 20,000,000 women 30-39 years of age. Based on the calculations presented in point 1, T-Scan will identify about 5.33% as high risk and yield a detection rate of 0.75% in this group (0.49% to 1.03%): about 1,066,000 (5.33% of 20,000,000) are classified as high risk and about 7995 (0.75% of 1,066,000) of them would have breast cancer.

If 1,066,000 women were selected from a population of 20,000,000, we would expect 0.15% or 1599 out of 1,066,000 to have cancer. The 95% confidence interval around the 0.15% rate in the sample of 1,066,000 is 0.14% to 0.16% (1492 to 1705 women).

We conclude that the cancer rate in the T-Scan positive "at risk" cohort is significantly higher than the rate in a randomly selected cohort of the same size.

We note that these calculations were performed based on a full population of women at risk; the confidence intervals in the random group depend on the sample size selected from that population.

Peer Reviewed Publications

Panel Pack Pages 280-281 Redacted Due to Copyright Issues

Redacted Presentations:

Davies RJ, Quinn DA, Davisson TH. Impedance spectroscopy characterizes the electrical signature of benign and malignant breast epithelium. San Antonio Breast Cancer Symposium; presentation # 6005; 2004.

Davies RJ, Quinn DA, Davisson TH. Alterations in transport and conductance during malignancy in breast epithelium. San Antonio Breast Cancer Symposium; presentation # 6009; 2004.

AD_____

Award Number:

W81XWH-05-2-0011

TITLE:

Electrical Impedance Scanning (EIS) for the Early Detection of Breast Cancer in Young Women

PRINCIPAL INVESTIGATOR:

Alexander Stojadinovic, M.D.

CONTRACTING ORGANIZATION:

USA MED RESEARCH ACQ ACTIVITY
820 Chandler Street
Fort Detrick, MD 21701-5014

REPORT DATE:

January 2006

TYPE OF REPORT:

Annual report covering period 12-20-2004 to 12-19-2005

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT:

X Approved for public release; distribution unlimited

Distribution limited to U.S. Government agencies only;
report contains proprietary information

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
20-01-2006	Annual Report	20-12-2004 to 19-12-2005

4. TITLE AND SUBTITLE
Electrical Impedance Scanning (EIS)

for the Early Detection of Breast Cancer in Young Women

5a. CONTRACT NUMBER
W81XWH-05-2-0011

5b. GRANT NUMBER
W81XWH-05-2-0011

5c. PROGRAM ELEMENT NUMBER
N/A

6. AUTHOR(S)
Alexander Stojadinovic, M.D.

5d. PROJECT NUMBER
N/A

5e. TASK NUMBER
N/A

5f. WORK UNIT NUMBER
N/A

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

WRAMC
6900 Georgia Ave, NW
Washington, D.C. 20307

8. PERFORMING ORGANIZATION REPORT NUMBER

HJF/WRAMC Annual 001

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Henry M. Jackson Foundation for the
Advancement of Military Medicine
1401 Rockville Pike, Suite 600
Rockville, Maryland 20852

10. SPONSOR/MONITOR'S ACRONYM(S)
HJF

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Background: Currently, no established method exists for screening young, pre-menopausal women for breast cancer. Electrical Impedance Scanning (EIS), an innovative breast screening technology, appears to identify women at increased risk for breast cancer.

Aim: A multi-center trial in the North Atlantic Region has been initiated in an effort to extend the potential benefit of this new technology to active-duty service members and young female healthcare beneficiaries with the aim of acquiring the data necessary to determine the feasibility of the EIS system, T-Scan™ 2000ED as a breast cancer risk identifying/screening tool in young women.

Methods: Women age 30 to 45 underwent EIS with routine clinical breast examination. EIS+ women were referred for further diagnostic breast imaging and breast biopsy, if indicated.

Results: 1,385 women were studied. Three women had a high risk or cancerous tumour of the breast; one was T-Scan positive. Of the 1,382 with benign findings, 1,285 were T-Scan negative. Thus, our interim results are consistent with an earlier validation trial showing that a T-Scan positive woman is six times more likely to have a high-risk lesions or cancer (~1 in 100) than a T-Scan negative women (~1 in 600).

Conclusion: Continuation of the present multi-center trial is warranted to confirm that EIS can identify young women at increased risk for breast cancer, those most likely to benefit from more diligent surveillance, early breast imaging, and risk reduction intervention.

15. SUBJECT TERMS
Breast cancer; screening; risk identification; electrical impedance scanning

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE		10	Alexander Stojadinovic, M.D.
					19b. TELEPHONE NUMBER *(include area code)* 202 782 9691

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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

Table of Contents

Introduction

PROBLEM:
Cancer accounts for one third of all illness-related mortality in the United States Army. Breast cancer, specifically, is the most common cancer in women and a leading cause of cancer death among those under the age of 40. Mammography, the gold standard for breast cancer screening in women over 40, is of limited use in younger women who typically have dense breast tissue, which is difficult to visualize with standard mammography. Widespread mammographic screening of younger women is further restricted because of concerns regarding the cumulative dose of radiation to which patients would be exposed on an annual basis.

Due to the limitations of mammography in younger patients, women under age 40 are generally not referred for breast imaging unless they are at elevated risk for breast cancer based upon a known familial risk factor. Unfortunately, 90-95% of breast cancers occur in "average-risk" women without known risk factors such as family history and gene mutations. Thus, a technology like Electrical Impedance Imaging (EIS), which is designed to more consistently and reliably identify "at risk" women by specifically analyzing individual tissue characteristics, would present the clinical community with an opportunity to offer additional surveillance to those 95% of women who are undetected by the current standard of care. The EIS system would thus be used to refer this at-risk subset of women for early breast imaging such as MRI (considered highly accurate in detecting early-stage breast cancer in high-risk young women), further follow-up, and risk-reduction measures (such as taking Tamoxifen).

This technology is of specific interest to us because over 92% of active duty women in the United States Army are under 40 years of age and over 50% are either African American or Hispanic. Race and ethnicity are considered important factors in breast cancer detection because death rates from breast cancer in the Army and in the community at large are higher for African American and Hispanic women than for Caucasian women.

The only standard breast cancer-screening tool for young women is clinical breast exam (CBE); however, CBE suffers from low true-positive and high false-positive rates and is not effective in detecting breast cancer at an early stage. In general, cancers discovered by clinical breast exam tend to be more advanced, and require a treatment regimen that is more aggressive, expensive, demanding and often less successful.

The impact of missed breast cancer in young women is considerable. In fact, women under age 50 account for more than 40% of all life years lost to breast cancer. And, as many studies have shown, the economic, social and emotional costs to families and the community are especially grave when young women die of breast cancer. The impact of this illness is especially significant in a military setting where each patient is also a critical component of our fighting force. Since early detection is critical to improved patient outcomes, the development of methods to promote early detection of breast cancer in younger women is widely recognized as a pressing clinical need.

TECHNOLOGY:
Routine screening with Electrical Impedance Scanning (EIS), a new technology that measures electrical signal flow across breast tissue, is under investigation for the

non-invasive detection of tissue current flow abnormalities associated with an increased risk for the development of breast cancer.

The goal of evaluating young women with EIS is risk identification that leads to additional imaging and early detection of breast cancer before it can be found by the current, decidedly inadequate screening method – clinical breast examination. The T-Scan™ 2000ED is a painless, radiation-free, rapid, no-risk breast-scanning device that is easy to use and doesn't require specialized training to interpret. The device consists of a portable flat screen monitor and a computer. A metal cylinder held in the woman's hand opposite the breast being examined is connected to the computer. A low-level, electrical signal is transmitted from the cylinder up the musculature of the arm, across the pectorals, and through each breast. The electrical current is measured on the breast with a non-invasive surface probe. The final EIS result is binary [suspicious (high-risk) –or– not suspicious (low-risk)], is entirely calculated by the computer software, and is immediately available to the examiner.

Initial results of a study of 2,035 young women undergoing T-Scan™ 2000ED EIS exam along with clinical breast exam indicate that an EIS positive woman is more than six times as likely as the average woman to have breast cancer. Further large-scale studies are needed to confirm that EIS can identify young women at increased risk for breast cancer, those most likely to benefit from more diligent surveillance, early breast imaging, and risk-reduction intervention.

Body

PROPOSED FIELD TESTING:
Breast tissue evaluation with EIS, as incorporated into the T-Scan™ 2000ED system, has enormous potential for our young female healthcare beneficiaries in terms of early detection, survival, active-duty force health promotion and disease prevention. Further testing of this technology is warranted and feasible within the Army based on the unique demographics of the active-duty population and the inherent deficiencies of using clinical breast examination alone to screen young women under the age of 40. This need is especially evident in the African-American and Hispanic patient population, which makes up nearly half of our fighting force.

A five-center, 5-year trial in the North Atlantic Region has been initiated in an effort to assess the potential benefit of this new technology to active-duty service members and young female healthcare beneficiaries with the aim of acquiring the data necessary to determine the feasibility of T-Scan™ 2000ED as a screening tool in young women

STUDY AIMS:
The present IRB-approved clinical trial uses electrical impedance scanning technology (T-Scan™ 2000ED) in order to address a unique research question, *Can tissue-based bioelectrical changes be utilized to reliably identify young women at increased risk of breast cancer?*

STUDY METHODOLOGY:
We have initiated a multi-center prospective clinical study of young women age 30 to 45 years who undergo annual physical cancer screening examinations. Study participants who

have completed informed consent undergo clinical breast exam (CBE), followed by EIS with the latest version of T-Scan™ 2000ED. Women who are positive on T-Scan are referred for further breast imaging, and if indicated as a result of the follow-up procedure, they undergo breast biopsy.

Summary of Results

Five centers (Walter Reed Army Medical Center; DeWitt Army Community Hospital, Ft Belvoir; Kimbrough Ambulatory Care Clinic, Ft Meade; Keller Army Hospital, West Point; Malcolm Grow Air Force Medical Center, Andrews AFB) are participating in this prospective multi-center clinical trial evaluating electrical impedance scanning (EIS) for breast cancer risk identification in young women.

As of December 31, 2005, there were **1,393 women** enrolled in the study. Table 1 demonstrates the ethnic diversity of the study population.

Table 1: Ethnic Origin of Study Participants

American Indian/ Alaskan Native	Asian	Native Hawaiian or Other Pacific Islander	Hispanic	Black	White	Multiracial	Other	Total
8	53	10	76	337	897	11	1	1,393

Adverse Events:

There were no reported cardiac, neurological, dermal, thermal or allergic reactions or adverse events, nor any reports of patient discomfort. This outcome echoed similar findings in the previous pilot (n=1,103) and validation (n=2,035) studies and in more than 10,000 prior examinations with the predecessor T-Scan 2000 device as reported in the previously approved PMA (FDA) application.

Study participant age and follow-up after EIS Screening Exam:

Distribution of study subjects according to age, EIS, radiological referrals (and suspicious findings), and biopsy referrals (and high-risk or cancerous diagnoses) are shown in Table 2.

Table 2: Follow-Up by EIS Outcome and Age

Scan	Age	Total	US	(Susp.)	MX	(Susp.)	MRI	(Susp.)	BX	(High-risk, Cancer)
EIS+	<40	49	8	0	37	0	32	0	0	0
	40+	49	4	0	46	0	37	2	3	1
EIS-	<40	747	47	4	82	4	17	0	5	0
	40+	540	62	6	378	7	21	2	13	2

US – ultrasound; MX – Mammogram; MRI – Magnetic Resonance Imaging; Susp. (Suspicious); BX – breast biopsy

Pivotal findings:

The T-Scan positive rate was 7.1%, with 1,385 women completing the EIS examination. The risk for biopsy-proven cancer or high-risk lesion in T-Scan positive patients is ~1 in 100, six times greater than the ~1 in 600 risk for T-Scan negative patients. Table 3 summarizes the EIS outcomes.

Table 3: EIS Outcomes

EIS result	Cancer or high-risk lesion	No cancer or high-risk lesion	Total
Positive	1	97	98
Negative	2	1,285	1,287
Total	3	1,382	1,385

Interpretation of Results

EIS (T-Scan) Screening Model:

In reviewing the T-Scan breast cancer risk stratification model, a clear and accurate description of the device's clinical utility may be illustrated via a comparative analysis of absolute risk for breast cancer in each of several patient populations. Specifically, absolute risk in the target or intended use population of young women can be compared with the absolute risk in other populations that are typically offered mammography.

It is presumed that if the T-Scan exam can identify women who are at an absolute risk for breast cancer that is equal to or greater than that of older women who are routinely offered mammography, the clinical benefit of this EIS screening approach should be evident.

The Routinely Screened Population, Women over 40:

Breast cancer screening guidelines endorsed by The National Cancer Institute, the American Cancer Society, the American College of Radiology and the U.S. Preventive Services Task Force all recommend annual mammograms for women over 40. The yield of mammographic screening is generally measured as the number of mammograms performed per cancer detected. Measured across the decade between age 40 and 49, approximately 300 to 400 mammograms are performed per detected breast cancer. The absolute risk in this age group is thus ~1 in 350 or approximately 0.0028. This level of absolute risk is therefore considered the "minimal screening threshold".

The Unscreened Population, Women under 40:

The American population of women under 40 accounts for nearly 11,000 breast cancers each year – equal to the total number of all cervical cancers in all ages annually diagnosed in the United States. Nonetheless, the low overall prevalence precludes mammographic screening of average risk women on a routine basis. Specifically, about 1.5 cancers are detected per 1,000 women between age 30-39 yielding an absolute risk of approximately 0.0015,

considerably less than the accepted risk minimal screening threshold for annual mammography screening in women 40+ years of age. Thus women under 40 continue to rely upon clinical breast exam alone for breast cancer screening.

The T-Scan Population, Categorizing Young Women as "Low risk" or "At risk":

By pre-screening average risk women in the target population as part of an annual well woman screening exam, the EIS screening intends to sub-classify (segment) the pool of young women into a "low risk" pool and an "at risk" pool. Importantly, the "at risk" sub-population should be at an absolute risk that is equal to or greater than the risk at which women are routinely screened with mammography, the minimal screening threshold.

Given a sensitivity of 33% and a specificity of 93% for the identification of high-risk lesions or breast cancer as evidenced in the on-going clinical trial and assuming a patient pool of 10,000 patients and 15 cancers (consistent with published prevalence data), T-scan risk stratification would proceed in the following manner:

T-Scan Negative patients, "low risk":

The pool of 10,000 patients yields 9,300 T-Scan Negative patients (93% of 10,000) and includes 10 "missed" cancers (67% of 15). Thus the absolute risk in the low-risk group is 1 cancer per 930 patients or 0.0011. This level of risk is significantly below the average risk in the target population and only a third of the minimal screening threshold.

T-Scan Positive patients, "at risk":

The pool of 10,000 patients yields 700 T-Scan Positive patients (7 % of 10,000) and includes 5 "detected" high-risk lesions or cancers (33% of 15). Thus the absolute risk in the "at risk" group is 1 cancer per 140 patients or 0.0071. This level of risk is significantly above the average risk in the target population and over three times greater than the absolute risk at which we commonly screen women over age 40.

Key Research Accomplishments

INTERIM ANALYSIS:
During the first six months of the five-year trial launched in the summer of 2005 we tested 1,385 young women. Three had a high-risk or malignant tumor of the breast; one was T-Scan positive. Of the 1,382 with benign findings, 1,285 were T-Scan negative. Thus, our interim results are consistent with an earlier validation study of 2,035 young women undergoing T-Scan™ 2000ED EIS exam along with clinical breast exam showing that an EIS positive woman is more than six times as likely as the average woman to have breast cancer.

The interim results of the current study indicate that a T-Scan positive woman is six times more likely to have a high-risk lesion or cancer (~1 in 100) than a T-Scan negative women (~1 in 600).

Reportable Outcomes

FUNDING APPLIED FOR:
Defense Acquisition Challenge Program (DACP) – A proposal to DACP has been submitted in order to allow the continuation and completion of this study.

Conclusions

The findings of the present prospective multi-center NARMC regional breast cancer screening trial are consistent with those of a prior EIS validation study indicating that women undergoing breast cancer screening with positive T-Scan are at increased risk of having breast cancer.

The interim results of the current study indicate that a T-Scan positive woman is significantly more likely to have a high-risk lesions or cancer than a T-Scan negative woman. This level of absolute risk compares favourably to the minimal screening threshold for mammography screening and may justify early breast imaging in women under age 40.

Implications

This study represents an important step involving adaptation of existing EIS technology for use under novel investigational clinical application: T-Scan for the identification of young women at high-risk for breast cancer.

We are exploring the efficacy of using EIS as an integral part of the screening process, a screening process that is widely recognized as deficient currently when examining young women with clinical breast exam alone during periodic office visits to the gynecologist or the primary care physician.

T-Scan is very safe, as there were no reported cardiac, neurological, dermal, thermal or allergic reactions or adverse events, or any reports of discomfort among over 4,000 women studied thus far with this device.

Our healthcare beneficiaries regard screening young women for breast cancer as extremely important, and they are very satisfied with the comfort, safety, and rapidity of T-Scan. The success of this proposed novel-screening paradigm (Breast T-Scan + Clinical Breast Exam, if proven efficacious) will likely increase awareness and compliance of required annual mammographic screening when a women reaches age 40.

More importantly, early detection of breast cancer through EIS-directed risk assessment and early breast imaging would translate into less aggressive treatment, more rapid return to duty, improved quality of life and survival in our young female healthcare beneficiaries.

Recommendations

Continuation of the present multi-center trial is essential to confirm that EIS can indeed consistently identify young women at increased risk for breast cancer – those that are most likely to benefit from more diligent surveillance, early breast imaging, and risk reduction intervention.

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