SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Multi-frequency Impedance Breast Scanner

Device Trade Name: T-Scan 2000

Applicant's Name: TransScan Medical, Inc.
70 Hilltop Road, Suite 2300
Ramsey, NJ 07446

PMA Number: P970033

Date of Panel Recommendation: August 17, 1998

Date of Notice of Approval to the Applicant: April 16, 1999

II. INDICATIONS FOR USE

The T-Scan 2000 is intended 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 is not intended for use in cases with clear mammographic or non-mammographic indications for biopsy. This device provides the radiologist with additional information to guide a biopsy recommendation.

III. CONTRAINDICATIONS, WARNINGS and PRECAUTIONS

Contraindications:

None.

Warnings/ Precautions:

Patient Management

The T-Scan 2000 (T-Scan) has not been studied on patients with implanted electronic devices, such as pacemakers. Because pacemakers detect low level electrical signals, there may be interference from the T-Scan, causing possible malfunction of the implanted device. Therefore the T-Scan is not recommended for use on such patients.

The T-Scan does not replace conventional methods for detecting or diagnosing breast cancer, such as mammography, clinical breast examination, ultrasound, or biopsy evaluation, when appropriate.

The T-Scan is not intended for use as a screening device for breast cancer. While the T-Scan has been shown to be effective in evaluation of lesions identified by other modalities, its use in detecting and evaluating lesions *not* identified by other modalities has not been fully studied.

Cases with clear mammographic or non-mammographic indications for biopsy should not be evaluated with the T-Scan. Based on the ACR BI- RADS lexicon, clear mammographic indications for biopsy include:

Linear and/or branching calcifications;
Clustered punctate or pleomorphic calcifications;
Masses with ill-defined or spiculated border; and
Clear architectural distortion.

Utility and results obtained with the device varies among users, based in part on the users' patient management methods. Thus, in the management of an individual patient, the attending physician should determine if a T-Scan should be performed and how to interpret T-Scan results.

Any additional finding suggesting possible additional lesions (in the vicinity of a previously identified lesion) is not considered a positive finding if there is no corresponding mammographic finding.

In order to avoid its misinterpretation as a border artifact, the T-Scan probe should be placed so that any focal abnormality is located away from the edge of the detector. If a patient has had recent breast surgery at the targeted site, T-Scan examination of that site should be deferred until complete healing occurs (typically about three months after surgery), as the surgical wound may present an impedance artifact.

The T-Scan probe should not be used on subjects with breached skin or open sores on the breast area. Doing so may increase the risk of transmission of infection between patients (see technical warning below and user's manual).

The influence of hormonal changes connected with the menstrual cycle on T-Scan results has not been fully studied.

The safety and effectiveness of a T-Scan examination has not been established in pregnant patients.

The T-Scan is designed to be used only in hospitals or clinical settings by medical professionals who have satisfactorily completed the start-up phase of the TransScan

Clinical Training program for the T-Scan. A follow-up training 30 to 60 days after completion of the initial phase is also required.

Technical

The T-Scan must be used only in accordance with the complete instructions for use provided.

In order to prevent electrical shock, do not remove covers or panels of the T-Scan.

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

After each examination always thoroughly clean the T-Scan Scan probe with mild detergent and alcohol to remove residual gel or conductive material. Failure to do so may result in the probe producing inaccurate recordings and possible disease transmission.

IV. DEVICE DESCRIPTION

T-Scan is a real-time, noninvasive imaging device for breast examination, based on mapping the local electrical impedance properties of breast tissue. Detection of cancer is based on the large inherent differences in capacitance and resistance between neoplastic tissue and surrounding normal tissue. Differences by factors of 10 to 50 between normal adipose tissue and malignant tissue have been reported by *in vitro* measurements on freshly excised breast tissue. T-Scan maps the local distribution of tissue electrical impedance in a range of frequencies from 50 - 20,000 Hz, by applying a minuscule electrical signal (approximately 1 volt) via a reference electrode on the body, and detecting the resulting impedance values at each of 256 sensors in a 16x16 array on a probe pressed against the breast. Hardware and software controls limit the voltage and the resulting current to safe levels (2.5 V and 5 mA maximum).

For each frequency, the electrical capacitance and conductance (the inverse of the resistance) at each sensor are computed and converted to gray scale -- high values are displayed as light shades of gray, and low values as dark shades. The resulting 16x16 map (high resolution), or 8x8 map (standard resolution), comprises one "sector" image of the portion of the breast under the probe. This image is processed using standard interpolation methods to produce a smoothed picture. During real time viewing, used while adjusting placement of the probe, a single frequency is used, typically pre-set by the factory, but may be selected by the operator. When recording the image, the set of different signal frequencies is recorded in rapid sequence. The factory protocol records a pre-set number of distinct signal frequencies in the specified range, although it can be modified by the operator via the system software to include any or all of 50 pre-programmed frequencies ranging from 50 - 20,000 Hz.

The impedance images are displayed as pairs of gray-scale maps: when viewing the standard display, one image represents capacitance, and the other conductivity. The exact gray scale mapping function is typically preset by the system software (using factory pre-set values or alternatives set by the operator), but is also operator adjustable on screen, so as to enhance the differences among the measured values.

In the normal breast, moderate variations in impedance values reflect the differences in the inherent impedance of various types of breast tissue in the vicinity of the sensor electrodes. A malignant tumor typically has very substantially increased capacitance and conductance compared to variations in the surroundings, and its presence results in a bright region on the displayed image.

The display parameters are adjusted (either by automatic pre-sets in the protocol or by manual adjustment by the examiner) so as to enhance small local impedance deviations from their surroundings. When replaying previous recordings, the image typically shows the impedance map at any one of the frequencies recorded. The operator can select which frequency is to be displayed. Alternatively, the operator can choose to display an image representing parameters derived from data acquired at several different frequencies.

V. ALTERNATIVE PRACTICES AND PROCEDURES

Other modalities used in the detection and diagnosis of breast lesions include clinical breast examination, mammography, sonography, magnetic resonance imaging, nuclear medicine, computed tomography, surgical biopsy, core biopsy and fine needle aspiration.

VI. MARKETING HISTORY

The Israel Ministry of Health approved the T-Scan in October 1995 for sale in Israel as an adjunct to conventional breast examination methods. The device received a CE mark on November 21, 1997. The T-Scan 2000 has also been approved for use in Greece (1997) and in Russia, Korea and China (1998).

As of January 1999, systems were installed and operating at approximately 41 sites in Israel, the United States, Europe (France, Italy, Greece, Russia and Germany) and Asia (China and South Korea), including 11 sites that participated in clinical studies. T-Scan has not been withdrawn from the market in any country.

VII. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

No adverse events have been reported during the pre-market clinical trials, or in commercial use in any of the countries where the T-Scan has been sold to date.

VIII. PRE-CLINICAL AND CLINICAL FEASIBILITY STUDIES

A. Tissue Impedance Studies

Since the 1920's, various researchers have reported malignant tissue to have substantially different electrical properties from those of normal tissue based on *in vitro* studies[1-5] and more recently on *in vivo* studies[6-8]. These studies have shown that malignant tissue typically has a much higher dielectric constant (capacitance) and conductivity than normal tissue, with malignant tissue reported to have values as high as 10-50 times those of the normal tissue.

B. Predecessor Device

Based on the above, the Mammoscan (predecessor of T-Scan 2000) was developed and pilot tested in the early 1980's, at the Weizmann Institute of Science in Rehovot, Israel. After laboratory testing and calibration, the device was tested on mastectomized breast samples to confirm impedance values comparable to published studies. The Mammoscan was then used in a clinical pilot study in Israel.[9-11] Clinical studies of the Mammoscan were commenced in Pistoia, Italy and the results published.[12]

C. T-Scan versus Mammoscan

The T-Scan was developed as a next generation version of the Mammoscan, using the same types of inert materials and gels as in the Mammoscan, preserving the core measurement basis and the same type of sensors as used the Mammoscan. TheT-Scan was tested on the same type network of capacitors and resistors to confirm comparable measurements to those obtained by Mammoscan. T-Scan added improvements reflecting newer technology, including real time imaging, increased resolution and frequency range, increased display area, simultaneous display of capacitance and conductivity images, spot view screen with corresponding anatomic map, and full hard copy and database capabilities.

IX. SUMMARY OF CLINICAL STUDIES

A. Overview of Clinical Studies

The intended usage mode of the T-Scan 2000 involves several key elements: identification of suspicious lesions by mammography or palpation; T-Scan examination targeted to the vicinity of the location of the suspicious lesion, with examination of other areas as necessary to confirm lesion location and to rule out artifacts and normal variants; identification of the suspicious lesion on T-Scan image; and adjunctive interpretation of the T-Scan image jointly with the mammogram.

To test the safety and efficacy of T-Scan as an adjunct to mammography, three studies were performed:

- Blinded Study: A prospective, double blind study was performed at seven centers in the United States, Europe and Israel, to test whether T-Scan alone detects cancer better than chance, and whether adjunctive re-reading of T-Scan images, together with the corresponding mammographic images, results in improved diagnostic accuracy when compared to that of mammography alone. T-Scan and mammographic examinations and interpretations were performed blindly, *i.e.*, without knowing if the patient was referred to biopsy, or the results of any other tests. Blinding of mammographic findings was done to standardize the mammographic information between centers and to avoid bias being introduced by knowledge of the results of other tests. Blinding of T-Scan results was also done to avoid bias, as well as to allow estimation of the accuracy of the T-Scan alone.

  Results from 504 biopsy cases showed that the blinded T-Scan examination detected cancer better than chance and that the blinded T-Scan adjunctive accuracy (sensitivity and specificity) was statistically significantly greater than the blinded mammographic accuracy. Thus, the Blinded Study documented the fundamental clinical utility of the T-Scan. Nevertheless, this study did not quantify the diagnostic accuracy of T-Scan in actual intended use, since targeted examination, a vital part of the T-Scan process, was precluded by the requirement for blinding, and in actual clinical practice mammograms are not interpreted without knowledge of clinical history, previous studies for comparison, and results of palpation.

- Targeted Study: As a part of the T-Scan exam when conducted according to intended use, the T-Scan probe is targeted to the area of a lesion identified by mammography or clinical examination. This mode of use, which provides the examiner with real-time feedback and allows for probe and breast manipulation to obtain maximum proximity to the suspicious lesion, maximizes the chance of detecting an abnormal lesion while minimizing detection of false positive spots due to normal variants. The objective of the study was to evaluate the accuracy of the T-Scan when targeted to the suspected lesion, in contrast to the Blinded Study. The Targeted Study, conducted at two centers in Israel and involving 657 cases, demonstrated that the T-Scan had greater sensitivity and specificity in targeted use than it did in the Blinded Study. Adjunctive readings of T-Scan results together with mammography, however, were not performed in the Targeted Study.

- Intended Use Study: A study was conducted of 74 consecutive biopsy cases at the one study center (Pistoia, Italy) where T-Scan was approved for clinical use in its full intended mode (targeted examination and adjunctive

interpretation), permitting estimation of the adjunctive accuracy of the T-Scan plus mammography versus that of mammography alone. The Pistoia Study directly demonstrated improvements in diagnostic accuracy when the T-Scan was used in its intended mode. In cases with equivocal mammograms (LOS 2 and 3), the Pistoia Study showed statistically significant improvements in sensitivity and specificity with adjunctive T-Scan over mammography alone.

A Bayesian multinomial-logistic model was used to combine data from the Pistoia Study, the Targeted Study, and the Blinded Study. This model provided additional statistical evidence of the improvement in diagnostic accuracy (both sensitivity and specificity) associated with use of the T-Scan in intended use. This model was also used to project the effect of use of T-Scan on cancer detection and biopsy referral in the indicated patients from a screening population.

B. Multicenter Blinded Study

1. Introduction

A multicenter study was designed to test the hypothesis that adjunctive combination of T-Scan with mammography can provide diagnostic accuracy significantly better than mammography alone.

2. Protocol

Study Design

The Blinded Study was carried out in 7 clinical centers in the USA, Europe and Israel. A total of 2,456 patients, including 882 scheduled for biopsy, were recorded by T-Scan and mammography in blinded fashion, *i.e.*, each imaging procedure was performed and interpreted without knowledge of the results from any other imaging modality or patient information except age. A final Test Set comprised of 504 biopsied breasts (179 malignant, 325 benign) was available for blinded re-reading. The Test Set was re-read and scored "blindly" using T-Scan images alone, using mammograms alone, and using adjunctive combination of mammogram and T-scan images. Each of the scores was compared against results of biopsy.

T-Scan Examination

A trained examiner followed a standardized computer-guided recording sequence on all patients, providing a standard 9 sector (3x3 matrix) frontal view of each breast. Recording started with the nipple in the center, and proceeded according to an automatic preset order guided by the system. After the nipple sector, recording moved to the upper outer sector and proceeded around the breast from lateral to medial. If no abnormal findings were found, the exam was ended. Any

specific abnormal areas not coinciding with normal anatomic features were to be further investigated by switching to the Spot Screen of the T-Scan 2000. The probe was placed so that the suspected area was centered within the target region of the probe.

Blinded Rereading

Panels of 40-60 patients each were organized for blinded rereading of the T-Scans and mammograms. The panels were comprised of patients with both malignant and benign biopsy results, as well as screening patients that did not undergo biopsy. The screening patients prospectively selected from each center were added to the panels so that the readers could not assume that all patients had suspicious mammographic findings.

T-Scan Interpretation

The following interpretation rules were used to evaluate T-Scan images:
Negative (normal) finding: The normal frontal T-Scan image is homogeneous dark gray, with no focal luminous areas in either the capacitance or conductivity image, except for:

- Bright nipples seen with reasonable symmetry in both breasts.
- Areas of dim-to-moderate or focal brightness seen symmetrically in both breasts, due to proximity to underlying cartilage and bone, or pectoral muscles.
- In large breasts, a long and moderately bright horizontal region extending through at least one sector in the lower margin of one or both breasts, associated with the inframammary ridge.
- Skin moles appearing as very bright spots.

Positive (abnormal) finding: Appearance of one or more of the following features in either the conductivity image, the capacitance image, or both:

- Bright Spot or Region: In addition to the two nipples, there is at least one discernible focal brightness or bounded region that is clearly more luminous than its surroundings and there is no corresponding spot or region in a symmetrical location on the contralateral breast.
- Gross Nipple Asymmetry: One nipple is considerably brighter or larger than the other.

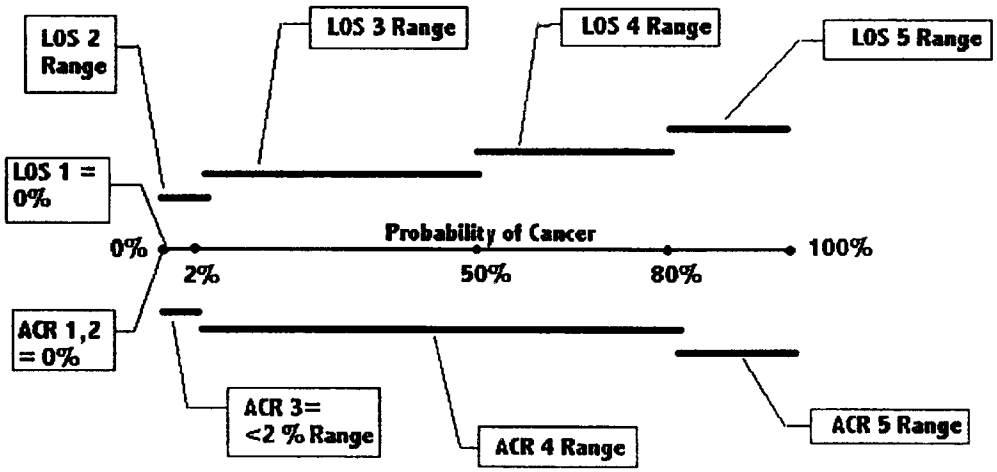
Although both breasts were viewed for detection of asymmetry between breasts, each breast was scored as a separate entity, with overall LOS score for each breast.

Artifacts: Contact artifacts are recognized as dark regions in the periphery of a sector and are bounded on their inner side by a bright border. Bubbles are recognized as dark spots with immediately attached bright spots which sometimes surround them. Luminous spots located at the margin of a sector are also assumed to be artifactual.

Mammogram Interpretation

The mammograms were blindly re-read by the examiners (all of whom were experienced mammographers) and scored without the T-Scan image information. The mammography results were assigned a score corresponding to a Level of Suspicion (LOS) of 1 to 5. The approximate relationship between this LOS and the ACR BI-RADS categories, in terms of probability of malignancy, is shown in Figure 2.

Figure 2. Correspondence between ACR BI-RADS and LOS, with approximate ranges of probability of malignancy



Adjunctive Interpretation

The mammograms were read jointly with the T-Scan images and results were compared to those with mammograms alone. The procedure for T-Scan adjunctive scoring was as follows:

- Review the mammogram in the corresponding vicinity of T-Scan finding and update the mammographic LOS score if there is a new focal finding as a result;

- If the mammogram has no focal finding, or if the T-Scan finding is equivocal, the adjunctive score equals mammographic score;

- If there is a focal mammographic finding, review the T-Scan image in the designated vicinity corresponding to the location of the finding; and

- Adjunctive score equals: mammographic score +1, if there are one or more bright regions in the vicinity or if there is nipple asymmetry, or mammographic score -1, if there are no bright regions and no nipple asymmetry.

Readers prospectively assigned LOS values for T-Scan, mammogram, and adjunctive reading, as if an LOS of 3 or more were the criterion for referring patients to biopsy. Biopsy was the "gold standard" for diagnostic accuracy. Results of the T-Scan, mammography and adjunctive readings were compared to the biopsy results in order to evaluate relative diagnostic accuracies.

3. Population

(a) Enrolled Patients

A total of 2,456 subjects were enrolled, including 1,574 screening patients and 882 biopsy patients whose breasts were imaged by T-Scan and mammography at the seven clinical centers shown in Table 1.

Table 1: Participating Centers

Center	No. Patients	No. Screening Patients	No. Biopsy Patients
Univ. of Massachusetts Medical Center Worcester, MA	208	161	47
Faulkner Hospital Boston, MA	194	88	106
Allegheny General Hospital Pittsburgh, PA	714	472	242
Sinai Hospital Detroit, MI	81	53	28
Hadassah Hospital	341	195	146

Center	No. Patients	No. Screening Patients	No. Biopsy Patients
Jerusalem, ISRAEL			
Clinique St. Catherine Avignon, FRANCE	794	564	230
Inititut Bergonie Bordeaux, FRANCE	124	41	83
Total	**2456**	**1574**	**882**

(b) Evaluated Patients

Of the 882 biopsy patients, 401 were excluded by prospective exclusion criteria, including unavailability of the original mammogram and incomplete T-Scan image. In the remaining 481 patients, 504 breasts were biopsied and were the focus of data analysis in this study.

(c) Baseline Characteristics

Several factors are potentially associated with the diagnostic accuracy of T-Scan images, particularly patient age, menopausal status and use of estrogen therapy, size of tumor, and breast size. Presented in Table 2 are the distribution of these factors for the 504 cases with biopsy results. Statistical analysis showed no significant differences between the US and non-US demographic distributions.

Table 2: Baseline Characteristics

Factor	N	%
Age (years)		
<40	52	11
40-49	149	31
50-59	118	25
60-69	103	22
70+	57	12
Not Recorded	23	
Total	504	100
Mean (SD)	53.8 (12.6)	
Range	16-90	
Menopausal Status		
Pre-menopausal	231	46
Post-menopausal	273	54
Total	504	100
Estrogen Therapy		
Yes	112	22
No	392	78
Total	504	100
Breast Size		
A cup	47	10
B cup	174	38
C cup	156	34
D cup	85	18
Not Recorded	42	
Total	504	100

Factor	N	%
Tumor Size (mm)		
0-5	47	14
6-10	98	30
11-15	66	20
16-20	48	15
>20	67	21
Not Recorded	178	
Total	504	100
Mean (SD)	15.4 (12.1)	
Range	0.5-100	
Palpable Mass		
Yes	186	45
No	226	55
Not Recorded	92	
Total	504	100

4. Study Duration

The study was conducted between May 1995 and March 1997.

RESULTS

5. Safety

All patients enrolled in the study who had a T-Scan examination were queried for evaluation of the safety of the T-Scan. Patients were asked whether they felt any discomfort, electric shock, or other adverse reactions during the examination. There were no reported cardiac, neurologic, dermal, thermal, allergic reactions or other adverse events. There were no reports of patient discomfort.

6. Effectiveness

(a) Statistical Methods

Indices of Diagnostic Accuracy for Cancer Detection

Sensitivity for each of the three methods (T-Scan alone, mammogram, adjunctive T-Scan reading) was calculated as the percent of malignant cases that was detected as positive (LOS 3 or more). Specificity was calculated as the percent of benign cases (LOS 1 or 2) that were detected as negative. Positive predictive value was calculated as the percentage of cases with positive findings (LOS 3, 4, or 5) which turned out to be malignant. Negative predictive value was calculated as the percentage of cases with negative findings (LOS 1 or 2) which turned out to be benign.

McNemar Test of Statistical Significance for Adjunctive Score

To characterize the net impact of the adjunctive score on the diagnostic result, as compared with mammography, adjunctive positive/negative scores were cross-tabulated versus mammographic positive/negative scores in 2 x 2 tables. Separate 2 x 2 tables were formed for biopsy positive, and for biopsy negative cases. For each table, the cases on which the mammogram and adjunctive score differed (the off-diagonal elements in the table) were examined to determine whether the adjunctive score was the correct one or the incorrect one. The p-values for the differences between mammography and adjunctive T-Scan, as shown in the results below, were determined by the McNemar test (exact binomial method) of the off-diagonal terms.

(b) Results

A total of 504 biopsied breasts, consisting of 179 malignant and 325 benign findings, were evaluated by all three methods (T-Scan alone, mammogram, adjunctive T-Scan).

Distribution of Mammographic Scores

Table 3 shows the LOS scores assigned by the readers for the mammogram. There were 273 equivocal lesions (LOS 2 and 3), constituting 54% of the total cases.

Table 3: Mammographic Score Distribution

LOS	1	2	3	4	5	Total
N (%)	50 (10)	111 (22)	162 (32)	124 (25)	57 (11)	504 (100)

Overall Diagnostic Accuracy

T-Scan Detects Cancer Better than Chance

A summary of sensitivity and specificity for the entire test set is shown in Table 4. T-Scan detected cancer with accuracy better than chance ($p < 0.0001$) with a sensitivity of 68% and specificity of 47%. By comparison, mammography had a sensitivity of 82% and a specificity of 39%. For women under 50 years age (Table 3-13 below), T-Scan had a sensitivity of 76% and a specificity of 51%, whereas mammography had a sensitivity of 69% and a specificity of 41%.

Table 4: Overall Results Summary: All Mammographic LOS (N=504)

	T-Scan alone	Mamm. alone	Adjunctive T-Scan	McNemar p-Value (Mamm. vs Adjunctive)
Sensitivity (Biopsy pos.=179)	68%	82%	88%	0.01
Specificity (Biopsy neg.=325)	47%	39%	51%	0.0003
PPV	42%	43%	50%	0.02
NPV	73%	80%	89%	0.03

Adjunctive Improvement in Diagnostic Accuracy

As an adjunct to mammography, T-Scan improved specificity from 39% to 51% (p=0.0003). Mammographic sensitivity of 82% increased to 88% with the adjunctive T-Scan reading (p=0.01). Positive predictive value increased significantly from 43% for mammography to 50% for adjunctive (p=0.02), while negative predictive value also increased from 80% to 89% (p=0.03).

Cases with Equivocal Mammograms

An important subpopulation are those cases having equivocal mammograms (LOS 2 or 3). Since the cutoff between a negative and a positive result was prospectively defined to be between LOS 2 and 3, and since in most instances, the adjunctive T-Scan reading could only increase or decrease the mammographic finding by one LOS unit, the cases for which the adjunctive use would affect patient management were those with mammographic LOS of 2 or 3 (on blinded re-reading).

The results for the 273 mammographically equivocal cases are presented in Table 5. Specificity increased significantly (p=0.0003) with adjunctive reading, for a net reduction of nearly 30% in false positive rate. Sensitivity was also significantly increased (p=0.02), for a 55% relative reduction in false negative rate. For these equivocal cases, the T-Scan reading alone had higher sensitivity and specificity than did mammogram alone.

Table 5: Results for Equivocal Mammograms (N=273)

	Mamm. alone	T-Scan Adjunctive	McNemar p-value (Mamm vs. djunctive)
Sensitivity (Biopsy pos.=50)	60%	82%	0.02
Specificity (Biopsy neg.=223)	41%	57%	0.0003

Analysis of Factors Correlated with Diagnostic Accuracy

Among the factors which could potentially influence the ability of impedance imaging to detect malignant tumors are age, menopausal status, tumor size palpability, and estrogen status. Table 6 below provides summary data for each subgroup of patients categorized according to these factors.

Table 6: Diagnostic Accuracy by Subgroup

	Sensitivity		Specificity	
Factor	**Mammogram**	**Adjunctive T-Scan**	**Mammogram**	**Adjunctive T-Scan**
Age <50 yrs	68%	85%	41%	53%
Age >50 yrs	86%	87%	35%	48%
Pre-menopausal	79%	82%	40%	55%
Post-menopausal	88%	88%	37%	46%
Palpable lesion	78%	84%	41%	51%
Non-palpable	81%	88%	44%	50%
Tumor size<1 cm	76%	84%	44%	58%
Tumor size>1 cm	85%	88%	40%	54%
Estrogen	78%	87%	34%	38%
No Estrogen	82%	86%	41%	54%

7. Conclusions

The protocol for this study required that both mammogram and T-Scan examinations and interpretation be conducted without knowledge of the results of other tests. Results from the Blinded Study showed improvement in diagnostic accuracy with adjunctive use of the T-Scan as compared to mammography alone.

C. Targeted Study

1. Introduction

As part of the recommended mode of T-Scan use, the examiner directs or targets the T-Scan probe to the area of the mammographic or palpable finding, and the reader interprets the targeted T-Scan image. This is known as "targeted use" and was employed in the Targeted Study described below. In this study there was no adjunctive reading of the mammogram with the T-Scan, as was done in the Blinded Study and as is part of the intended use of the device.

In this study, the T-Scan examiner had knowledge of the position of the abnormal finding on mammographic or clinical examination, so that the T-Scan probe could be positioned appropriately for the area of concern.

2. Methods

Patient Population

The patient population examined in these centers can be briefly described as follows:

- Elisha Hospital: All 583 consecutive, biopsy patients from January, 1995 to August, 1997 who had histology results from biopsy, gave informed consent, and had a T-Scan examination.

- Hadassah Hospital: All 74 consecutive, biopsy patients from March to December, 1997 who had histology results from biopsy, gave informed consent, and had a T-Scan examination.

Baseline Characteristics

The two Targeted Study center populations were similar in age composition to each other and to that of the Blinded Study. The two centers had somewhat lower prevalence of cancer (23% in Elisha, 24% in Hadassah) than the Blinded Study (36%). The two centers had a median lesion size of 15 mm, and had comparable ranges of lesion size. The Blinded Study had a median lesion size of 13mm, which was not significantly different from that of the Targeted Study.

T-Scan Examination and Interpretation

Interpretation of the T-Scan images was performed at the time of the examination (Elisha) or by re-reading blinded to biopsy results (Hadassah). The reader knew that each patient was to undergo biopsy, and also knew the location of the lesion found by other tests, but did not know the histological findings of any biopsy performed. No adjunctive interpretations were made with the mammograms and T-Scan images, nor any was adjunctive score assigned by the readers.

3. Results

The key patient characteristics and results for the Targeted Study is summarized in Tables 7 and 8 below. The T-Scan accuracy figures refer to the results for the T-Scan alone, as there was no adjunctive score. Unlike the Blinded Study, results are presented for all lesions combined, since the purpose of this study was to evaluate the effect of T-Scan targeting on diagnostic accuracy as compared to a blinded T-Scan examination. There is no reason to assume that the effect of T-Scan targeting compared to blinded T-Scan examination would depend on the LOS of the mammogram.

Table 7: Patient Characteristics in Targeted Study

	Elisha	Hadassah	All
Total lesions	583	74	657
Malignant	132 (23%)	18 (24%)	150 (23%)
Benign	451 (77%)	56 (76%)	507 (77%)
Lesion Size (mm)			
Range	3 to 80	7 to 70	3 to 80
Median	15	15	15
SD	8.9	12.5	9.4
Age			
Range	21 to 86	23 to 81	21 to 86
Mean	53.7	51.9	53.5
SD	12.0	12.5	11.9

Table 8: Targeted T-Scan Accuracy in Targeted study

	Elisha	Hadassah	All
Total lesions	583	74	657
Sensitivity			
All Lesions	77%	83%	78%
Palpable	85%	80%	85%
Non-Palpable	74%	85%	75%
Specificity			
All Lesions	68%	54%	67%
Palpable	67%	61%	66%
Non-Palpable	69%	50%	67%

4. Conclusions

Targeting improves the sensitivity and specificity of the T-Scan exam as evidenced by comparison to the results from the T-Scan alone in the Blinded Study.

D. Pistoia Hospital Intended Use Study

1. Introduction

Data were collected from T-Scan examinations performed at Pistoia Hospital between June 1997 and December 1998, corresponding to the period of time during which biopsy results were reliably available at the Breast Center.

The T-Scan examinations were performed according to intended use, that is, the T-Scan examination was targeted at lesions previously identified by mammography or physical exam and the T-Scan interpretation was done adjunctively.

2. Methods

Patient Population

Women were primarily self-referred to the breast clinic for routine clinical examination and/or mammographic screening. All patients from June 1997 to December 31, 1998, who were scheduled for biopsy were potential candidates for the study, and were asked to give informed consent. Particular efforts were made to recruit biopsy candidates who had equivocal findings on mammography or clinical examination. The patients included in the study represent all patients seen during the study time period who gave informed consent, had the required biopsy information, and had a T-Scan examination. A small number of patients underwent biopsy of lesions based solely on prior family history of breast cancer, patient history, patient preferences, or other clinical findings, even though they were not found to be positive on mammographic or T-Scan examination.

Study Examinations

The Principal Investigator (PI) performed a complete clinical breast exam and a technologist performed a mammographic examination. In those cases where indicated, an ultrasound examination was also performed by the PI. The PI interpreted the mammogram and assigned an LOS score (1-5), although he was not blinded to the prior clinical examination and/or ultrasound findings, if any. In almost all cases, the mammographic examination preceded the T-Scan examination, except when the patient was not scheduled for routine screening mammography (primarily due to age being outside the screening range). In all cases, the PI assigned an LOS score based solely on mammographic findings, to the best of his ability.

The T-Scan examination was performed by a trained technologist. The targeted T-Scan examination was directed to the location of the suspected lesion, based on mammographic and/or clinical findings (and ultrasound findings, when performed

prior to the T-Scan examination). Additional views were obtained in instances where the T-Scan examination was negative in the vicinity of the suspicious lesion, or to obtain a better image of spots detected. Where a prior mammogram was available, the T-Scan examination took place while the mammogram was plainly visible on a nearby lightbox. The results of the examination were reported to the PI while the patient was still in the examination room, and if there were questions as to lesion identification or findings, additional T-Scan views were performed by the PI to resolve the questions.

T-Scan Interpretation

All T-Scan images were interpreted and scored solely by the PI at the time of examination. Focal brightness in the vicinity of the finding, and/or asymmetric nipples, was considered a positive finding. T-Scan adjunctive interpretation was performed in conjunction with review of the mammogram and with knowledge of prior findings.

3. Results

Records for a total of 74 patients with T-Scan results were analyzed representing all consecutive biopsy cases for which T-Scan examinations were performed during the indicated time period. The mean age of the patients was 57.9±13.6 years (range 17-81). The mean lesion size was 13.5±8.2 mm (range 1.0-50.0 mm).

Biopsy results were available for 72 cases, 57 were malignant and 15 were benign. Mammography results were available for 64 cases. The analysis described below (Table 9) includes those 36 cases where biopsy results, mammogram, and T-Scan were available and where the mammographic results were equivocal (LOS 2 or 3).

Table 9: Mammogram and T-Scan Accuracy for Pistoia Intended Use Study

	Mammogram	Adjunctive T-Scan	McNemar p-value
Equivocal Cases (LOS=2,3)			
Sensitivity	20/30 (66.7%)	28/30 (93.3%)	0.04
Specificity	3/6 (50.0%)	5/6 (83.3%)	0.50

4. Conclusions

This study demonstrates that a T-Scan examination performed according to intended use (including targeted recording and adjunctive interpretation) improves diagnostic accuracy as compared to mammography alone.

E. Combining Clinical Study Results

1. Background

As noted above, while the Blinded Study showed significant increases in diagnostic accuracy (both sensitivity and specificity) with adjunctive T-Scan ascompared to mammography, the T-Scan examination in that study did not include targeted recording. The Targeted Study was designed to evaluate the performance of the T-Scan 2000 when used in a targeted mode; however, it did not employ adjunctive readings. The Pistoia study, which employed targeted adjunctiveT-Scan reading, directly showed that intended use of the T-Scan 2000 results in a statistically significant increase in sensitivity compared to mammography. However, due to the small number of equivocal cases in the Pistoia Study which were determined to be benign, comparisons involving specificity were not statistically significant. A statistical model (described below) which combines data from the different studies is used to show that the diagnostic accuracy (both sensitivity and specificity) of the T-Scan in intended use is significantly better than mammography alone.

Statistical Model

Description

A Bayesian multinomial-logistic model was fit to the data for women with equivocal mammograms in the Pistoia Intended Use Study, the Targeted Study and the Blinded Study. This is a general linear model incorporating a multinomial outcome, a logistic link function, Bayesian prior probabilities and random effects to facilitate borrowing strength between the Pistoia study and the other studies.

The multinomial outcomes are the four probabilities corresponding to the four possible combinations of mammographic LOS (2,3) and T-Scan result (-,+). Biopsy status (benign, malignant) and study (Pistoia, Elisha, Hadassah, Blinded) are entered into the model as independent factors.

A random effects model was used which borrows strength from the Targeted and Blinded studies for estimating diagnostic accuracy of the T-Scan according to intended use, in part because of the small number of benign cases with equivocal mammograms in the Pistoia study. In this model, results from each center are compared, and to the extent that they are similar to one another, pooled together and used to adjust the results from each center.

Bayesian prior probabilities were used mainly to account for instances in which the raw counts input into the model were zero, as the non-Bayesian model gives spurious results for data with zero counts. Accordingly, Bayesian prior probabilities were assigned a random normal deviate with mean 0 and variance 0.33 (corresponding to the variance of the logarithm of a variable with a uniform distribution).

Outputs

In addition to modeling the multinomial probabilities, several differences between probabilities were calculated with this model, including the differences in true positive probability and false positive probability. These differences were, in turn, used to calculate differences in total number of negative biopsies and cancers detected. In these calculations cancer prevalence was conservatively assumed to be 10% in this population of women with equivocal mammograms.

Computational Method

The model fit and desired outputs are computed using BUGS (Bayesian inference Using Gibbs Sampling) software developed at Cambridge University, England (© MRC Biostatistics Unit 1997).

In addition to allowing specification of Bayesian prior probabilities, this software also performs Markov Chain Monte Carlo simulations to derive exact numerical solutions.

4. Results of the Model

The results of the statistical model, in terms of false positive rates, total negative biopsies, true positive rates, and cancers detected are presented in Table 10 below.

Table 10: Differences in probabilities, biopsies and cancers detected (TransScan minus Mammogram)

	Difference in Probability		
Outcome	Difference	95% CI	
True Positive Rate	0.156	(0.024,0.288)	P(>0)98.9%
False Positive Rate	-0.202	(-0.388,-0.009)	P(<0)98.0%

The results shown are summarized as follows:

- The T-Scan true positive rate (sensitivity) among women with equivocal mammograms (LOS 2 or 3) is estimated to be higher than the mammogram

true positive rate among these women by approximately 0.156. The probability that this figure is greater than zero is nearly 99%.

- The T-Scan false positive rate (1-specificity) among women with equivocal mammograms is expected to be lower than the mammogram false positive rate among these women by 0.202. The probability that this figure is greater than zero is 98%.

X. CONCLUSIONS DRAWN FROM THE STUDIES

The data provided are valid scientific evidence demonstrating the safety and effectiveness of the T-Scan 2000 for its indicated use. The various clinical studies demonstrate that use of the T-Scan 2000, as an adjunct to mammography, results in improved diagnostic accuracy when compared to mammography alone.

XI. PANEL RECOMMENDATIONS

At a meeting held on August 17, 1998, the Radiological Devices Panel recommended that the TransScan Medical, Inc. PMA for the T-Scan 2000 be considered approvable with the condition that the labeling be revised and that the company conduct a post-market study to evaluate the effects of the menstrual cycle on device performance.

XII. CDRH DECISION

CDRH concurred with the Radiological Devices Panel recommendation and issued a letter to TransScan Medical, Inc. on October 7, 1998 advising them that its PMA was approvable subject to the submission of additional information, including appropriate labeling, and a post-market study to evaluate the effects of the menstrual cycle on device performance. In subsequent amendments to the FDA, TransScan Medical, Inc. adequately addressed the conditions specified by the panel and the FDA. The applicant's manufacturing facility was inspected on July 28-30 and August 2-4, 1998 and was found to be in compliance with the Quality Systems Regulation. FDA issued an approval order on April 16, 1999.

XIII. APPROVAL SPECIFICATIONS

Directions for use: See attached Labeling.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Hazards to Health From Use of the Device: See Indications for Use, Contraindications, Warnings/Precautions, and Adverse Events in the attached labeling.

Within 60 days of approval, the sponsor must submit a protocol in the form of a PMA supplement for a postapproval study to determine the changes in sensitivity and specificity resulting from the use of the T-Scan in actual clinical practice for the targeted population, as well as the effect of other factors, such as menstrual cycle, on the accuracy of the T-scan output. A report of the findings must be submitted within one year as part of the sponsor's annual report.

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