T-Scan 2000 ED

Breast Cancer Risk Assessment for Women 30-39

PMA P050003

Obstetrics and Gynecology Devices Advisory Panel Meeting

August 29, 2006

Presentation Overview

• INTRODUCTION	Ron Ginor, M.D.
• PRODUCT OVERVIEW	Ron Ginor, M.D.
• PIVOTAL TRIAL	LTC Alexander Stojadinovic, M.D.
• INDEPENDENT STATISTICAL REVIEW	Joel Verter, Ph.D.
• EXPERT PANEL REPORT	Vivian Dickerson, M.D.
▪ Gynecology Comment	Vivian Dickerson, M.D.
▪ Radiology Comment	A. Thomas Stavros, M.D.
• CLOSING REMARKS	Ron Ginor, M.D.

Product Overview
T-Scan 2000 ED
Breast Cancer Risk Assessment for Women 30-39

Ron Ginor, M.D.
Mirabel Medical Systems

Public Health Need

- Breast cancer is the leading cause of cancer death in women 15-54
- Cumulative incidence of cancer is 1 in 229[1] women diagnosed by age 40
- Prevalence of breast cancer in women 30-39 is 1 in 667[2]
- Current Standard of Care is the clinical breast exam
  - Highly subjective, has limited sensitivity (0-100%)
  - Limited in small lesions
- Women without known risk factors under 40 not recommended for additional imaging
- 70-80%[3] of cancers in women under 40 are self-detected
- Breast cancer screening in young women is an important clinical need to address

1. National Cancer Institute. 2000. SEER cancer statistics review 1975-2000. Rockville, MD: U.S. Department of Health and Human Services.
2. Chalkowske K et al. 1993. Positive predictive value of screening mammography by age and family history of breast cancer. *Journal of the American Medical Association* 270:2444-2450.
3. Coates Rochat et al. 2001. Patterns and predictors of the breast cancer detection methods in women under 40 years of age (United States). Cancer Causes and Control 12:431-432.

Development Program

- Pilot Study
- Multi-center Pivotal Trial
- U.S. Army Medical Research Study (Ongoing)

Product Overview
T-Scan 2000 ED

- NOT a diagnostic test
- NOT a substitute for mammography or other imaging techniques
- It IS a risk assessment tool to aid in identifying younger women at increased risk for breast cancer missed by the current Standard of Care
  - **Complement to Clinical Breast Exam (CBE)**
  - **Identifies women at risk equivalence to those currently receiving mammography**
- Target population
  - **Women 30-39**
  - **Asymptomatic**
  - **CBE negative**
  - **No known high risk factors**
- All T-Scan screened patients would be missed by the current Standard of Care

Indication for Use

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

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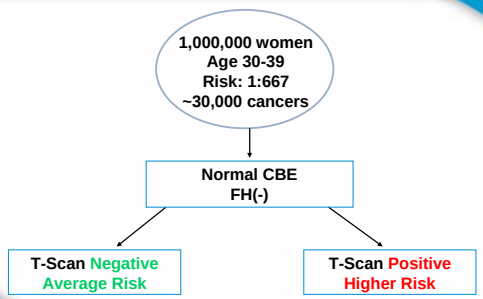
T-Scan Helps Detect Cancers Otherwise Missed



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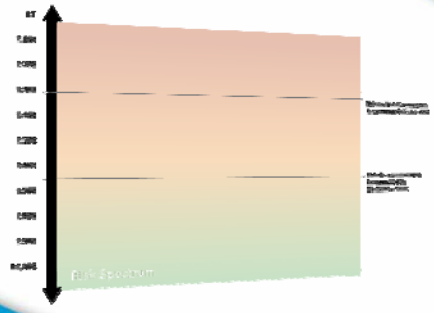
The T-Scan Risk Model

Identifying "at risk women" with T-Scan



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The T-Scan Risk Model

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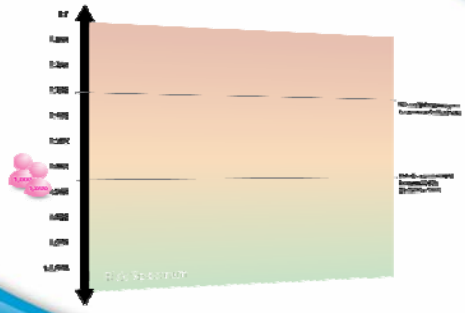

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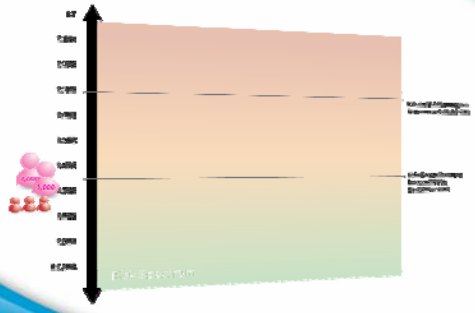
The T-Scan Risk Model

Identifying "at risk women" with T-Scan



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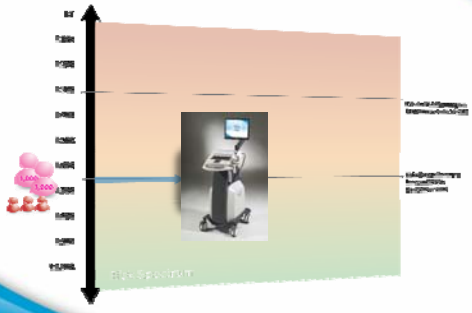
The T-Scan Risk Model

Identifying "at risk women" with T-Scan



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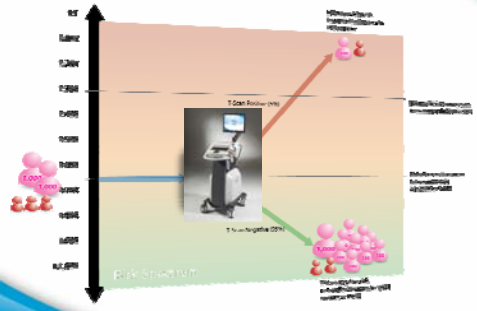
The T-Scan Risk Model

Identifying "at risk women" with T-Scan



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Device Description

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Electrical Impedance and Malignancy

- Association between electrical impedance changes and malignant cells recognized since 1926
- Differences in conductivity between benign and malignant breast tissue based on:
  - Water and electrolyte content, related to hormonal changes and to angiogenesis[1]
  - Changes in membrane permeability and polarization[2]
  - Changes in orientation and packing density of cells[1,3]

[1] Foster KR, Schwan HP. 1989. *Biomed Engineer* 17:25-104.
[2] Morucci JP et al. 1996. *Biomed Engineer* 24:275.
[3] Stuchly MA, Stuchly SS. 1990. *Biol Effects Med App Elect Ener.*

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Principle of the Technology

Electrical Impedance Scanning (EIS) of the breast applying Ohm's law

$$\text{(R) Resistance} = \frac{\text{(V) Voltage}}{\text{(I) Current}}$$

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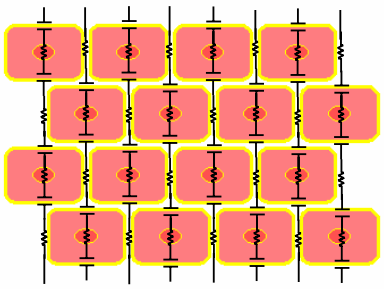
RC Model for Tissue



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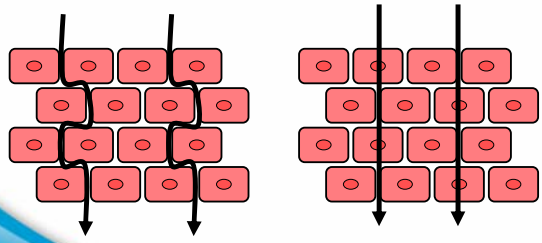
Frequency Dependent Current Flow



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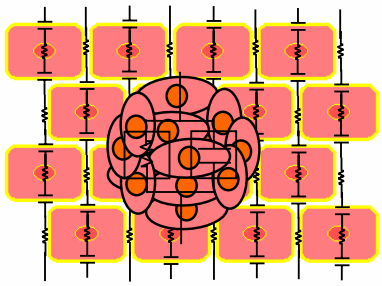
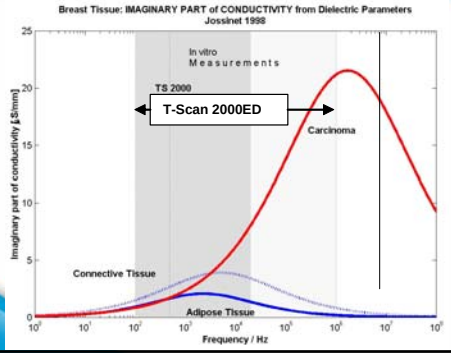
RC Model for Lesion in Tissue



Basis for EIS Detection of Cancer



Tissue Resistivity

Tissue	Resistivity
Blood	150 Ωcm
Muscle	530 Ωcm
Fat	2,060-2,720 Ωcm
Normal breast tissue	2,000 Ωcm
Cancer breast tissue	660 Ωcm

Technology History

- T-Scan based on FDA-approved TS2000 device
  - Intended for use as an adjunct to mammography to provide radiologist with additional information to guide a biopsy recommendation
  - Approved in 1999
  - Determined to be safe and effective
  - No safety concerns in clinical practice
- Clinical practice demonstrated high sensitivity for small cancers

TS2000 Demonstrated Improved Sensitivity for Small Masses

- Published data following approval showed the device was particularly good at discriminating between benign and malignant lesions when evaluating small (sub 2 cm) masses
  - Sensitivity was 93% for cancers < 10 mm, but only 65% for larger lesions (Diebold et al., RSNA 2003)
  - Sensitivity was 92% (N=98) for lesions < 10 mm (Fuchsjaeger et al., RSNA 2003)
  - Sensitivity was 71% for lesions < 20 mm but only 48% for larger lesions (Wersebe et al., 2002, Radiol 37:65-72)
  - Sensitivity was 100% (N=29) for lesions ≤ 10 mm but only 78% (N=28) for larger lesions (Kolb et al., RSNA 2002)
- This led the Company to recognize that aside from measuring the activity of known lesions, the device might be useful in sampling the entire breast and identifying malignant and pre-malignant cells in women too young for routine mammography

T-Scan 2000 ED

Features of the T-Scan 2000 ED

- Always
  - CBE always performed prior to exam
  - CBE results must be entered
- Cannot replace mammography in women over 40
- Cannot be used if pregnant
- Helps identify risk factors
- Binary result
  - No image

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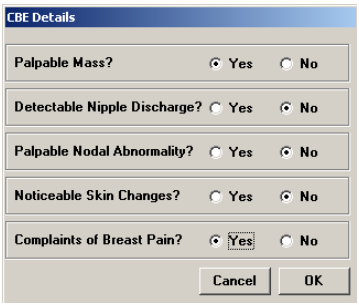
CBE Always Performed Prior to Exam



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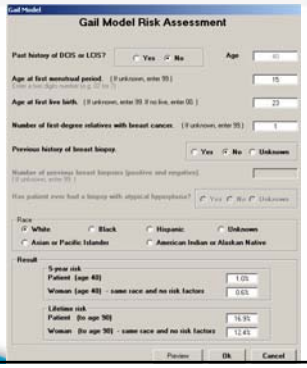
Gail Model



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Signal Transmitter

A low electrical signal is applied through the signal transmitter held in the patient's contralateral hand to the breast being examined

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Surface Probe

The resulting electrical current is measured on the breast by an array of 8x8 sensors

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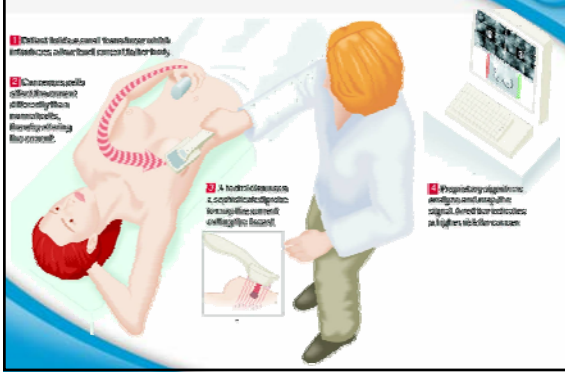
How does the T-Scan work?



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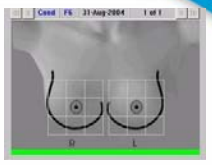
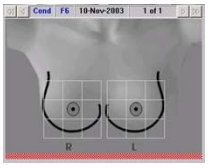
Display of Results

If exam results were within the normal range ("normal" or "negative"), a single green indicator bar was displayed



If exam results were outside the normal range ("suspicious" or "positive"), a single hatched red indicator bar was displayed



Pivotal Trial

LTC Alexander Stojadinovic, M.D.
Vice Chairman, Department of Surgery, Walter Reed Army Medical Center
Associate Professor of Surgery, Uniformed Services University of the Health Sciences, Washington, DC

Disclaimer

- Principal Investigator, Pivotal Clinical Trial
- The views expressed herein are those of the presenter and do not reflect the official policy of the Department of the Army, the Department of Defense or the U.S. Government

Pivotal Trial Study Design

- **Study Design:** Multi-center, prospective trial, 2 arms
- **FDA Input**
- **Study Objective:** Can physiologic differences in breast tissue of women age 30-39, as detected by T-Scan, be utilized as a predictor of breast cancer risk in a manner that is equal to, or better than, current risk assessment models?
- **Primary Outcome:** Relative probability of breast cancer
- Calculated from specificity, sensitivity and prevalence

Comparison of T-Scan to Standard Risk Assessment Criteria

Risk Factor	Risk Multiple	Reference
First degree relative with breast cancer	1.2-1.9	Collaborative Group on Hormonal Factors in Breast Cancer, 2001
Two first degree relatives with cancer	2.9	Collaborative Group on Hormonal Factors in Breast Cancer, 2001
Diagnosis of atypical hyperplasia	4.0	Collaborative Group on Hormonal Factors in Breast Cancer, 2001
BRCA gene mutation *(test performed in at-risk women)*	5.7	Schwab et al., 1998
T-Scan success threshold (prospectively defined)	**2.0**	**FDA Meeting of June 2, 2003**

Specificity Arm Clinical Sites

Principal Investigator(s)	Clinical Site
Mark Akin, MD	Austin Area Obstetrics, Gynecology, and Fertility, P.A. Austin, TX
Lora Larson, MD	Associated Women's Specialists Tulsa, OK
Richard Chudacoff, MD	Private gynecology clinic Sugar Land, TX
Mukul Singh, MD	Cornell University Medical Center New York, NY
Steven Domnitz, MD	Associates in Women's Healthcare Wayne, NJ
Ari Brooks, MD	Drexel University, Department of Surgery Philadelphia, PA

Specificity Arm Clinical Sites

Principal Investigator(s)	Clinical Site
Tamar Alweiss, MD	Hadassah Hospital Mount Scopus Jerusalem, Israel
Mal Margolin, MD	Helfond Medical Group Los Angeles, CA
LTC Alexander Stojadinovic, MD **COL Craig Shriver, MD**	Keller Army Community Hospital West Point, NY
William Dore Binder, MD	Louisiana Women's Healthcare Associates Baton Rouge, LA
Shlomo Mannor, MD	Private gynecology clinic New York City, NY
Robert Pulliam, MD	Professional Medical Ultrasonics Beckley, WV

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Specificity Arm Clinical Sites

Principal Investigator(s)	Clinical Site
Robert Mucciola, MD	East Hills Ob/Gyn Johnstown, PA
Michael Breen, MD	Travis OBGYN Associates Austin, TX
Ronald Wapner, MD	Drexel University Department of OBGYN Philadelphia, PA
LTC Alexander Stojadinovic, MD **COL Craig Shriver, MD**	Walter Reed Army Medical Center Washington, DC
Arieh Yeshaya, MD	Dailli Clinic
Moshe Shimonov, MD	Givataiim, Israel

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Sensitivity Arm Clinical Sites

Principal Investigator(s)	Clinical Site
Isaac Pappo, MD	Assaf HaRofe Hospital Tel Aviv, Israel
Curtis A. McClurg, MD	Austin Radiological Association Austin, TX
Owen Winsett, MD	Breast Center of Austin Austin, TX
Orah Moskovitz, MD	Bnei Zion Hospital Haifa, Israel
Ari Brooks, MD	Drexel University, Department of Surgery Philadelphia, PA
Rachel Brem, MD	George Washington University Washington, DC

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Sensitivity Arm Clinical Sites

Principal Investigator(s)	Clinical Site
Scott Fields, MD	Hadassah Hospital Mount Scopus Jerusalem, Israel
Fannie Sperber, MD	Ichilov Hospital Tel Aviv, Israel
Raymond Menassa, MD	Italian Hospital Nazereth, Israel
LTC Alexander Stojadinovic, MD **COL Craig Shriver, MD**	Keller Army Community Hospital West Point, NY
Sylvia Trumble, MD	Kelsey Siebold Clinic Houston, TX
William Dore Binder, MD	Louisiana Women's Healthcare Associates Baton Rouge, LA

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Sensitivity Arm Clinical Sites

Principal Investigator(s)	Clinical Site
Howard Karpoff, MD	Orange County Surgical Group Middletown, NY
Zahava Gallimidi, MD	Rambam Hospital Haifa, Israel
Ward Parsons, MD	Rose Featherwood Center Houston, TX
Ward Parsons, MD	Rose Joan Gordon Center Houston, TX
Daniel Mishell, MD	University of Southern California Los Angeles, CA
LTC Alexander Stojadinovic, MD **COL Craig Shriver, MD**	Walter Reed Army Medical Center Washington, DC

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Pivotal Study Arms

Specificity Arm Healthy Women	Sensitivity Arm Pre-Biopsy
	Enriched population
Evaluate: False Positive Rate (Specificity)	Evaluate: True Positive Rate (Sensitivity)
Women ages 30-39, T-Scan as part of a well-woman visit	Pre-menopausal women ages 30-45, expecting breast biopsy

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Specificity Arm
Inclusion/Exclusion Criteria

- Inclusion criteria
  - Women ages 30-39
  - Not pregnant
- Exclusion Criteria
  - Pregnancy
  - Hx chemotherapy
  - Hx breast biopsy within the preceding 90 days
  - Hx fine needle aspiration (FNA) within the preceding 30 days
  - Hx previous breast cosmetic surgery
  - Implanted electrical device (e.g., pacemaker)
  - Palpable lesion

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Sensitivity Arm
Inclusion/Exclusion Criteria

- Inclusion Criteria
  - Women ages 30-45 (age range expanded to include pre-menopausal women ages 40-45*)
  - Not pregnant
  - Scheduled for biopsy
- Exclusion Criteria
  - Pregnancy
  - Hx chemotherapy
  - Hx breast biopsy within the preceding 90 days
  - Hx fine needle aspiration (FNA) within the preceding 30 days
  - Hx previous breast cosmetic surgery
  - An implanted electrical device (e.g. pacemaker)

* Post-menopausal women excluded from analysis

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Sensitivity Arm
Enriched Population

- Use of enriched population (40-45) is essential and clinically sound
  - Rarity of CBE(-) tumors at ages 30-39
  - Initiation of screening mammography at age 40 not associated with particular breast tissue differences
  - Data on pre-menopausal women ages 40-45 in sensitivity arm are applicable to the intended use population
  - Looking for small, non-palpable lesions
- Post-menopausal women should be excluded from data analyses

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Data Analysis
Primary Endpoint

- Relative probability (R_p) calculation*
  - Estimate of specificity (S_p) from the Specificity arm
  - Estimate of sensitivity (S_n) from the Sensitivity arm
  - Prevalence (R_{ca}) = 1.5 cancers/1,000 women

* $R_p = S_n / [S_n(R_{ca} + (1- S_p)(1-R_{ca})]$

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Prevalence in Target Population
Conservative Estimate

Reference	Number of Women	Prevalence (cancers/1000 women)
Destouet & Sherman, 1997	4,402	1.1
Kerlikowske et al., 1993	**6,787**	**1.5**
Kerlikowske et al., 2000	43,906	1.8
Bobo et al., 2000	79,399	2.3
Kerlikowske et al., 1996	7,308	3.0

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Data Analysis
Secondary Endpoints and Covariates

- **Baseline variables**
  - Palpability (CBE normal/abnormal)
  - Contraceptive/Fertility/HRT/Other drugs (none, compounds with estrogen, compounds with progesterone only, Tamoxifen, other)
  - Family History (no 1st degree relatives with breast cancer, one or more 1st degree relatives with breast cancer)
  - Bra Size (A-B, C-D, >D)
  - Ethnicity (Caucasian, Black, Hispanic, Asian, American Indian)

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Pivotal Trial Results and Conclusions

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Primary Endpoint
Relative Probability of Breast Cancer

- Sensitivity: **26.4%** (95% CI = 17.4%-35.4%)
- Specificity: **94.7%** (95% CI = 93.7%-95.7%)
- Relative probability (R_p): **4.95** (95% CI = 3.16-7.14)*

* $R_p = 0.264 / [(0.264)(0.0015) + (1-0.947)(1-0.0015)]$

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Specificity Arm

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Specificity Arm
Patient Disposition

	Number of Patients
T-Scan exams attempted	**1,946**
Patient declined exam	2
Technical difficulties	14
T-Scan exam results	**1,930**
Exclusions	**179**
age <30	50
age >39	62
lactating	3
breast cosmetic surgery	3
chemotherapy	2
palpable lesion	59
Per protocol exams	**1,751**

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Specificity Arm
Baseline Characteristics
Per Protocol Analysis

Baseline Characteristic	N	%
Menopausal Status		
Pre-menopausal	1,718	98.1%
Post-menopausal	32	1.8%
Missing	1	0.1%
Age		
Mean (Std.)	1,751	34.7 (2.8) yrs
Range	1,751	30 – 39 yrs

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Specificity Arm
Baseline Characteristics
Per Protocol Analysis

Baseline Characteristic	N	%
Contraceptive/Fertility/HRT Drugs		
None	968	55.3%
Estrogen compounds	572	32.7%
Progesterone only compounds	96	5.5%
Other	31	1.8%
Missing	84	4.8%
Number of 1st Degree Relatives with Breast Cancer		
0	1,558	89.0%
1 or more	163	9.3%
Missing	30	1.7%

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Specificity Arm
Baseline Characteristics
Per Protocol Analysis

Baseline Characteristic	N	%
Race/Ethnicity		
Asian	26	1.5%
American Indian	9	0.5%
Black	51	2.9%
Hispanic	48	2.7%
Caucasian	1,358	77.6%
Missing	259	14.8%
Bra Size		
A or B	839	47.9%
C or D	794	45.3%
More than D	84	4.8%
Missing	34	1.9%

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Specificity Arm
Results by Subgroups

Baseline Characteristic	N	T-Scan Negative	Specificity	P value
Menopausal Status				**NS**
Pre-menopausal	1,718	1,626	94.6%	
Post-menopausal	32	31	96.9%	
Missing	1	1	100.0%	
Contraceptive/Fertility/HRT Drugs				**NS**
None	968	918	94.8%	
Estrogen compounds	572	543	94.9%	
Progesterone only compounds	96	88	91.7%	
Other	31	30	96.8%	
Missing	84	79	94.0%	

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Specificity Arm
Results by Subgroups

Baseline Characteristic	N	T-Scan Negative	Specificity	P value
CBE Result				**NS**
Normal CBE	1,751	1,658	94.7%	
Abnormal CBE	59	56	94.9%	
Number of 1st Degree Relatives with Cancer				**NS**
None	1,558	1,469	94.3%	
One or more	163	159	97.6%	
Missing	30	30	100.0%	

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Specificity Arm
Statistically Significant Factors

Baseline Characteristic	N	T-Scan Negative	Specificity	P value
Race/Ethnicity				**0.02**
Caucasian	1,358	1,284	95.6%	
Black	51	45	88.2%	
Hispanic	48	42	87.5%	
Asian	26	26	100%	
American Indian	9	9	100%	
Bra Size				**0.001**
A or B	839	812	96.8%	
C or D	794	740	93.2%	
More than D	84	76	90.5%	

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Specificity Arm
Overall Results

- Specificity in the per protocol population: **94.7%** (95% CI = 93.7%-95.7%)
- Range of specificity in subgroups (87.5%-100%)
- All ranges still within pre-specified criterion of 2.0 or greater

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Sensitivity Arm

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Sensitivity Arm
Patient Disposition

	Number of Patients
T-Scan exams attempted	**597**
Patient declined exam	4
Technical difficulties – no result	4*
No biopsy	44
T-Scan exam results	**545**
Exclusions	**155**
technical difficulties - result	66*
age <30	26
age >45	28
lactating	2
biopsy in preceding 90 days	1
chemotherapy	8
post-menopausal	24
Per protocol exams	**390**

*Cannot happen in clinical practice; due to study blinding

Sensitivity Arm
Technical Exclusions

- 65 of the 70 cases excluded due to technical difficulties were with two devices at one site
- Sites were recording "blind" (per agreement with FDA, at sensitivity sites, the device was programmed so as not to display the red/green result)
- Performance of the devices was not discovered immediately due to blinding

Sensitivity Arm
Baseline Characteristics
Per Protocol Analysis

Baseline Characteristic	Cancer Cases (N = 87)	
	N	%
Age		
30-39	37	42.53%
40-45	50	57.47%
Mean (Std)	87	39.5 (3.9) yrs
Range	87	30 – 45 yrs
Contraceptive/Fertility/HRT Drugs		
None	57	65.5%
Compounds with estrogen (with or without progesterone)	7	8.0%
Compounds with only progesterone	2	2.3%
Other	1	1.1%
Missing	20	23.0%

Sensitivity Arm
Baseline Characteristics
Per Protocol Analysis

Baseline Characteristic	Cancer Cases (N = 87)	
	N	%
Number of 1st Degree Relatives with Breast Cancer		
None	68	78.2%
One or more	13	14.9%
Missing	6	6.9%
Bra Size		
A and B	26	29.9%
C and D	34	39.0%
>D	3	3.4%
Missing	24	27.6%

Sensitivity Arm
Baseline Characteristics
Per Protocol Analysis

Baseline Characteristic	Cancer Cases (N = 87)	
	N	%
Race/Ethnicity		
Asian	2	2.3%
American Indian	0	0.0%
Black	7	8.0%
Hispanic	4	4.6%
Caucasian	74	85.1%

Sensitivity Arm
Baseline Characteristics
Per Protocol Analysis

Baseline Characteristic	Cancer Cases (N = 87)	
	N	%
CBE		
Normal CBE	17	19.54%
Abnormal CBE	70	80.46%
Lesion Size (mm)		
≤ 20	45	51.7%
> 20	27	31.0%
Missing	15	17.2%
Mean (Std)	72	22.9 (15.1)
Range	72	5-80

Sensitivity Arm
Results by Subgroups

Baseline Characteristic	N	T-Scan Positive	Sensitivity	P value
Patient Age				**NS**
30-39	37	7	18.9%	
40-45	50	16	32.0%	
Contraceptive/Fertility/HRT Drugs				**NS**
None	57	12	21.1%	
Estrogen compounds	7	2	28.6%	
Progesterone only compounds	2	1	50.0%	
Other	1	0	0.0%	
Missing	20	8	40.0%	

Sensitivity Arm
Results by Subgroups

Baseline Characteristic	N	T-Scan Positive	Sensitivity	P value
Number of 1st Degree Relatives with Cancer				**NS**
None	68	17	25.0%	
One or more	13	4	30.8%	
Missing	6	2	33.3%	
Bra Size				**NS**
A or B	26	4	15.4%	
C or D	34	8	23.5%	
More than D	3	2	66.7%	
Missing	24	9	37.5%	

Sensitivity Arm
Results by Subgroups

Baseline Characteristic	N	T-Scan Positive	Specificity	P value
Race/Ethnicity				**NS**
Caucasian	74	21	28.4%	
Black	7	2	28.6%	
Hispanic	4	0	0.0%	
Asian	2	0	0.0%	
American Indian	0	0	0.0%	

Sensitivity Arm
Results by Subgroups

Baseline Characteristic	N	T-Scan Positive	Sensitivity	P value
CBE Result				**NS**
Normal CBE	17	5	29.4%	
Abnormal CBE	70	18	25.7%	
Lesion Size				**NS**
≤ 20mm	45	16	35.6%	
> 20mm	27	6	22.2%	
Missing	15	1	6.7%	

Sensitivity Arm
Overall Results

- Overall sensitivity in the per protocol population: **26.4%** (95% CI = 17.4%-35.4%)
- No subgroups statistically significant
- Palpability (CBE+/-) did not affect sensitivity

Primary Endpoint
Relative Probability of Breast Cancer

- Sensitivity: **26.4%** (95% CI = 17.4%-35.4%)
- Specificity: **94.7%** (95% CI = 93.7%-95.7%)
- Relative probability (R_p): **4.95** (95% CI = 3.16-7.14)*

* $R_p = 0.264 / [(0.264)(0.0015) + (1-0.947)(1-0.0015)]$

Population Model

1,000,000 women
Age 30-39
FH(-)
Risk: 1:667
1,500 cancers

CBE Normal

T-Scan(-) = 94.7% of 1M (947K)
T-Scan false (-) = 74% of 1.5K (1.1K)

T-Scan(+): 5.3% of 1M (53K)
T-Scan true (+): 26% of 1.5K (400)

Average Risk
947,000 women
1,100 cancers
Risk: ~1:861

Higher risk
53,000 women
400 cancers
Risk: ~1:136

ALL T-Scan positive cases otherwise missed

Number of Mammograms Performed per Cancer Detected for Women Age 40-49 in the U.S.

Women Screened	Cancers Detected	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.

Literature suggests ~400 mammograms are performed per 1 cancer detected in women ages 40-49

Relative and Absolute Risk for Breast Cancer

Patient Population	Relative Risk for Breast Cancer (95% CI)	Absolute Risk for Breast Cancer	
T-Scan 2000 ED	**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	1:340*	0.0029

* Absolute Risk = (1 cancer / 400 mammograms) / 85% Sensitivity

Number of Screening Mammograms Needed to Detect 1 Cancer

Patient Population	Mammograms / Cancer Detected
Women age 40-49	~400
Average risk women age 30-39	952
T-Scan positive women	194

The number of mammograms needed to detect 1 cancer is substantially lower than that accepted under the current Standard of Care (screening mammography for women starting at age 40)

Independent Statistical Review

Joel Verter, Ph.D.
Senior Investigator, Statistics Collaborative, Inc.

Topics to Discuss

- Enrichment of Sensitivity arm
- Estimate of Specificity
- Effects on Relative Probability
- Pooling
- Israel vs. U.S.
- Subgroups
- Overall Conclusion

Enrichment of Sensitivity Arm

- **T-Scan is a device to screen not to diagnose**
- **Sensitivity arm needed to calculate sensitivity**
- **Sensitivity study screening process:**
  - Women 30-39
  - Exclude women with positive family history
  - Exclude women a positive clinical breast exam
- **All T-Scan positive women are identified for follow-up**
- **Those with lesion undergo breast biopsy**

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Enrichment of Sensitivity Arm

- **Without an enriched population, the Sensitivity arm would have required screening over 250,000 women 30-39 to identify the 87 biopsy-proven cancers**
- **Calculation:**
  - 87 / (1.5/1,000) = 58,000 (prevalence)
  - 58,000 / 0.264 = 219,697 (sensitivity)
  - 219,697 / 0.91 = 241,425 (palpability)
  - 241,425 / 0.96 = 251,485 (family history)

Conclusion: Sensitivity cannot be estimated without an enriched cohort

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FDA Statistics Slide 4
Pivotal Clinical Study Results

Pivotal Clinical Study Results

The sponsor's prospective, multi-center, 2-arm, pivotal clinical study enrolled 2,543 women, of which 2,165 completed the study per protocol.

	Specificity	Sensitivity
Specificity Arm	94.7%* (1658/1751) Not Verified – No Follow-up	Not available – No Follow-up
Sensitivity Arm	80.6%* (258/320)	26.5% (24/94)
Combined Arms	92.5% (1916/2071)	

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Estimate of Specificity

- **Design of Specificity arm allows for an appropriate estimate based on the screening algorithm**
- **Data collected in Sensitivity arm *allows* for a calculation for specificity**
- **Screening process in the Sensitivity arm is not appropriate for a specificity calculation**
  - Not because of CBE or other measures, but because the women have all been identified with a breast pathology
- **Conclusion: The estimate of specificity (false positive rate) from the Sensitivity arm will not estimate the false positive rate for the intended screening cohort**

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Components of Relative Probability

- **Prevalence**
  - The assumed rate of breast cancer in the population
- **Sensitivity**
  - The probability that the test result is positive in a woman who has breast cancer, i.e., the true positive rate, or cancer detection rate
  - Enriched population is desirable and necessary
- **Specificity**
  - The probability that the T-Scan result is negative in a woman who does not have breast cancer, i.e., the true negative rate
  - Estimate based on data from the Specificity arm is appropriate

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Effects of Different Estimates of Prevalence on Relative Probability

Spec(%)	Sens(%)	Prev(%)	Rel Prob
94.7	26.4	0.15	4.95
94.7	26.4	0.05	4.97

- **Prevalence**
  - 1.5 / 1,000 or 0.15% best estimate from the literature
  - 0.5 / 1,000 or 0.05% suggested in FDA presentation

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Effects of Different Estimates of Sensitivity on Relative Probability

Spec(%)	Sens(%)	Prev(%)	Rel Prob
94.7	18.9	0.15	3.55
94.7	17.6	0.15	3.31
94.7	11.2	0.15	2.11

- **Sensitivity**
  - 17.6% lower 95% C.L.
  - 18.9% 30-39 cohort
  - 11.2% all U.S. women

Effects of Different Estimates of Specificity on Relative Probability

Spec(%)	Sens(%)	Prev(%)	Rel Prob
96.8	26.4	0.15	8.16
87.5	26.4	0.15	2.11

- **Specificity**
  - 96.8% bra size A/B
  - 87.5% lowest in any subgroup in the Specificity arm

Pooling Across Sites Specificity and Sensitivity Arms

- **Implied by protocol design**
- **Multi-center study**
- **Common protocol at all sites**
- **Common device use training**
- **Uniform study conduct**
- **Binary exam outcome**
  - No interpretation of the outcome required

Pooling Across Sites Sensitivity Arm

- **Subgroup analyses issues:**
  - Evaluate heterogeneity of response among sites
  - Low power
  - Type 1 error
  - Post hoc analyses
- **Even under these circumstances, if heterogeneity is suggested by the data, further investigation is warranted**
  - Regulators, clinical investigators, and Sponsor should all encourage this analysis
  - Only by an open and honest attempt to explain any potential heterogeneity can the end user (i.e., the patient) be assured they are receiving the best care

Sensitivity by Site

N	Biopsy Positive	Proportion	P-Value
10	1	0.1	
16	5	0.31	
8	3	0.38	
4	1	0.25	
8	2	0.25	
15	8	0.53	p = 0.27
6	0	0	
1	0	0	
4	2	0.5	
2	0	0	
4	0	0	
1	0	0	
2	1	0.5	
3	0	0	
3	0	0	

Subgroup Analyses of Specificity

- **Subgroup analysis not pre-specified in protocol**
- **Three statistically interesting findings**
  - Bra size: A/B (97%), C/D (93%), >D (91%)
  - Ethnicity: Caucasian (96%), Black (88%), Hispanic (88%), Other (100%)
    - adjusted to U.S. census race distribution (93%)
  - Nation: U.S. (96%), Israel (93%)
    - Israeli sites ranked 11 and 14.5 for specificity
- **Conclusion: Data for all the specificity sites can be pooled**

Subgroup Analyses of Sensitivity

- FDA has noted possible difference in sensitivity for Nation
  - U.S. (11.5%)
  - Israel (32.8%)
- Statistically significant differences are likely a reflection of the fact there were few patients/site and few total cancers in the U.S.
- If the Israeli patients were excluded (both arms) the study would still meet its success criterion (Relative Probability = 2.3)

  Conclusion: Pooling the data from the sensitivity study is appropriate and justified

Multivariate Overall Logistic Regression Results

Effect by order entered into the logit model	FDA Estimated Adjusted OR (FDA slide 17)	Mirabel Estimated Adjusted OR
FH (Positive versus Negative)	3.6	1.5
Country (Israel versus US)	4.0	4.1
Hormone (Not Used versus Used)	3.3	3.8
Menopause (Post- versus Pre-)	4.8	4.8
T-Scan (Positive versus Negative)	2.6	2.6

Logistic Regression Results for Women Age 30-39

Effect by order entered into the logit model	FDA Estimated Adjusted OR (FDA slide 19)	Mirabel Estimated Adjusted OR
FH (Positive versus Negative)	5.5	1.4
Country (Israel versus US)	4.4	4.6
T-Scan (Positive versus Negative)	3.0	2.8
Hormone (Not Used versus Used)	2.6	3.0

Conclusion

- Logistic regression analyses strongly support the inference that a T-Scan positive woman is at increased risk for breast cancer
- It is demonstrated in the previous two slides that after adjustment for risk factors the OR indicates between a 2.5 and 3.0-fold increase in risk of breast cancer for a woman with a positive T-Scan

Overall Conclusions

- Based on my review of the data in both arms of this study, the results meet the conditions for approvability
  - Well designed
  - Well executed
  - Appropriately analyzed
  - Pre-specified success criterion met
- Shows clinical efficacy with no safety concerns

Expert Panel Report on Assessment of Breast Cancer Risk in Young Women with T-Scan 2000 ED

Vivian Dickerson, M.D., FACOG
Clinical Professor of General Obstetrics and Gynecology, University of California, Irvine; Past-President American College of Obstetricians and Gynecologists

Expert Panel Contributors

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  - **Vivian Dickerson, M.D., FACOG**
    Clinical Professor of General Obstetrics and Gynecology, University of California, Irvine; Past-President American College of Obstetricians and Gynecologists
  - **Steven R. Goldstein, M.D.**
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  - **Ronald J. Wapner, M.D.**
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Expert Panel Contributors

- **Radiology**
  - **David Gur, MS, Sc.D.**
    Executive Vice Chairman and Professor of Radiology, Department of Radiology School of Medicine, University of Pittsburg
  - **A. Thomas Stavros, M.D., FACR**
    Medical Director of Ultrasound, Radiology Imaging Associates, Director of Ultrasound, Sally Jobe Breast Center, Denver, Colorado
- **Surgical Oncology**
  - **LTC Alexander Stojadinovic, M.D.**
    Vice Chairman, Department of Surgery, Walter Reed Army Medical Center; Associate Professor of Surgery, Uniformed Services University of the Health Sciences, Washington, D.C.

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Expert Panel Contributors

- **Statistics**
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    Director, Statistics and Consulting Unit; Executive Director, M.A./Ph.D. Program in Biostatistics, Boston University; Executive Director of Data Management and Biostatistics, Harvard Clinical Research Institute; Director of Statistics, Framingham Heart Study
  - **Joel I. Verter, Ph.D.**
    Senior Investigator, Statistics Collaborative, Inc.
- **Epidemiology**
  - **Theodore Colton, Sc.D., M.S.**
    Professor, Epidemiology and Biostatistics, Boston University School of Public Health

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Expert Panel Assessment of the T-Scan

- **Carefully considered T-Scan breast cancer screening paradigm**
- **Evaluated the design and execution of pivotal study**
- **Assessed issues raised by FDA**
- **Considered if and how T-Scan can be incorporated within the Standard of Care for young women**
- **Provided written opinion to Panel**

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Expert Panel Conclusions

- **Large, well-designed study**
- **Appropriate to exclude post-menopausal women**
- **Appropriate enrichment of population in the Sensitivity arm**
- **Sufficient data presented on safety and effectiveness**
- **Results generalizable to U.S. target population of women 30-39**
- **Women identified as positive would otherwise be missed**
- **Approval will stimulate further development in an area that needs technological improvement**

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Gynecology Comment

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Standard of Care

- Current lack of effective screening tools for breast cancer in women under 40
- CBE, the Standard of Care, is variable and depends on:
  - Palpation procedure
  - Tumor size
  - Menopausal status
  - Breast density
  - Examiner proficiency
  - Breast size
  - Frequency
- Mammography not recommended to average risk women between ages 30-39

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Clinical Challenge

- Breast cancer in young women is a tremendous clinical challenge
- Most cancers in this age group are self-detected (71%)
- 5-year survival rate in younger women lower than in older women
- Early detection of breast cancer in young women is a clinical challenge

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Early Risk Assessment

- T-Scan, a screening device, not a diagnostic device
- Desirable attributes of a screening tool include
  - Reasonable sensitivity – ability to detect disease when present
  - High degree of specificity – if disease not present, test is negative
  - Uniform quality and repeatability
  - Easy to perform
  - Non-invasive with low morbidity and high safety
  - Acceptable to women
  - Widely available

ACOG testimony before The Society for the Advancement of Women's Health Research, September 30, 2003.
IOM/National Academy of Sciences, 2001.

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Early Risk Assessment

- Identifying women at higher risk can lead to early detection and diagnosis
- Early detection means:
  - Less expensive treatment
  - Less aggressive treatment
  - Improved quality of life
  - Improved long-term survival

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Conclusion

- T-Scan helps identify 3,000-5,000 cancers that would have been otherwise missed using the current Standard of Care
- T-Scan is a safe and effective technology that addresses an important unmet need in women's health

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Expert Report

Radiology Comment

A. Thomas Stavros, M.D., FACR
Medical Director of Ultrasound, Radiology Imaging Associates, Director of Ultrasound, Sally Jobe Breast Center, Denver, Colorado

Radiology Comment

- Similarity of Breast Tissue in Women Ages 30-39 and Ages 40-45
- Clinical Management
  - Mammography
    - Film Screen
    - Digital
  - Other Imaging
    - MRI
    - US
- Absence of Risk
  - Comparison to Standard of Care
  - Calculated

Similarity of Breast Tissue in Women Ages 30-39 and Ages 40-45

- In my experience, there is no detectible radiographic difference in breast tissue between women ages 30-39 and ages 40-45 as long as all are pre-menopausal
- Virtually all imaging studies must develop an appropriate enrichment mechanism
- Most studies group together all pre-menopausal women under age 50
- No radiological reason to expect that there would be a disparity or lack of concordance between the enriched arm (extended to age 45) and the target population (age 30-39)

Clinical Relevance of T-Scan ED Result

Risk Factor	Risk Multiple	Reference
First degree relative with breast cancer	1.2 - 1.9	Collaborative Group on Hormonal Factors in Breast Cancer, 2001
Two first degree relatives with breast cancer	2.9	Collaborative Group on Hormonal Factors in Breast Cancer, 2001
Diagnosis of atypical hyperplasia	4.0	Collaborative Group on Hormonal Factors in Breast Cancer, 2001
BRCA gene mutation *(performed in at risk women)*	5.7	Schwab et al., 1998
Prospectively defined success threshold	2.0	FDA Meeting of June 2, 2003
T-Scan positive in Pivotal Trial	**4.95 (2.79, 7.14)**	**PMA Data (Amendment II)**

Mammographic Sensitivity: Film Screen and Digital

- FDA quotes the Pisano DMIST Study
  - I think the sensitivity reported is too low
- Quote from Pisano et al. 2005
  - "Why were the sensitivities of both digital and film mammography measured in this study apparently lower than the sensitivities in other studies?" (21-23)
  - "Utilized 455-day follow-up…but the use of the 455-day follow-up interval for reporting estimates of diagnostic accuracy is unconventional"
  - References listed by Pisano:
    - Poplack et al. (72.4%)
    - Banks et al. (86.6%)
    - Smith-Bindman et al. (77%)
  - A conventional estimate of sensitivity is in the range of 70%-80%
  - The Pisano article also clearly suggests that FF Digital mammography is best for women under age 50
    - **Sensitivity expected 78% if FFD is used with 365 day follow-up**

Clinical Management of T-Scan Positive Women: Other options

- **US**
  - **Awaiting ACRIN 6666 Study**
- **FFDM-US**
  - **One visit**
    - **Same room, same equipment, same technologist**
  - **Adds only a few minutes to exam**
  - **Decreases call back**
- **MRI**
  - **Often performed in women having less risk than measured in the T-Scan pivotal study**
    - **ADH, LCIS and ALH (RR ~ 4.0)**
    - **Approved by CMS, paid by Medicare**
  - **No radiation risk**
  - **Excellent in dense breast**

Benefit/Risk Analysis

- There is no point in reestablishing the benefit/risk calculation for T-Scan positive patients
  - The Standard of Care is clearly established for patients at higher risk
    - Histological: ADH, LCIS
    - Family history, Gail score
    - BRCA, genetic testing
- Mammography presents no notable risk to patient
- Other imaging methods present no notable risks to patient
- Benefit: new cancers detected
- Direct risk: None

Conclusion: T-Scan is a safe and effective technology that addresses an important unmet need in women's health. We have accepted means for working up such patients and routinely do so.

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Mirabel MEDICAL SYSTEMS

Closing Remarks

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Conclusions

- Well-conducted, multi-center study
- Primary endpoint exceeded pre-specified success criterion
  - Risk probability > 2.0 for per protocol population and all subgroups
- Highly favorable benefit-risk ratio
  - No product safety issue
  - No additional mammography risk
  - Long-term (5 year) study ongoing
    - Federally-funded U.S. sites
    - 2,500 patients thus far

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Algorithm Stability Full Dataset

Group	Sensitivity		Specificity	
	Mean (# cases)	95% CI	Mean (# cases)	95% CI
Verification	34 (18)	12-56	90 (691)	84-96
Validation	29 (12)	3-55	87 (263)	79-95
PMA Intent to treat	28.9 (90)	19.9-37.9	94.7 (1933)	93.7-95.7
PMA Per protocol	31.4 (70)	20.4-42.4	94.9 (1751)	93.9-95.9
***PMA Per protocol (A02)**	26.9 (87)	17.9-35.9	94.7 (1751)	93.6-95.8

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Questions Posed by FDA Clinical Significance

- Subgroup analyses do not alter conclusions
- All subgroup analyses meet the success criterion of study (RP ≥ 2.0), including U.S. vs. Israel
- T-Scan identifies a cohort of patients at or above the risk level of those already referred for mammography

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Questions Posed by FDA Enrichment

- Enrichment is appropriate
  - Age does not matter (pre-menopausal 40-45)
  - EIS technology valid independent of age
  - Sensitivity better in smaller lesions
  - Not related to palpability
  - Inversely related to size

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Questions Posed by FDA
U.S. vs. Israel

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

- Israel and U.S. sites can be pooled, based on statistical and clinical criteria
- Both countries alone exceed RP of 2.0

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Questions Posed by FDA
Technical Difficulties

- T-Scan at one U.S. site accounted for 92.9% of failures
- Due to blinding of investigators
- Impossible to alter results manually
- Could never happen in clinical practice

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Questions Posed by FDA
Potential Risks of Mammography

- Contemporary mammography equipment offers negligible risk
- Absolute risk for breast cancer in women 40-49 is 0.0029
- Absolute risk for breast cancer in T-Scan positive women 30-39 is 0.0073
- Mammographic screening of T-Scan positive women is more than 3 times as effective as the current standard of care for women 40-49

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