P050003
T-Scan 2000 ED

Introduction

Robert Phillips, Ph.D.
Chief, Radiological Devices Branch
Office of Device Evaluation
August 29, 2006

Proposed Indication for Use

Indicated as a complement to Clinical Breast Exam (CBE) in asymptomatic women age 30-39 (inclusive) with a negative CBE and negative family history (FH) for breast cancer.

Early Breast Cancer Detection
Current Standard of Care – Average Risk Women

Organization	Age	Physical	Imaging
ACS/ACR/NCI	20-39	CBE at least every 3 years	
	≥ 40	CBE every year	Mammogram annually
US Preventative Services Taskforce	≥ 40	± CBE every 1-2 years	Mammogram every 1-2 years
ACOG	40-49	CBE every year	Mammogram every 1-2 years
	≥ 50	CBE every year	Mammogram annually
AMA	40-49	CBE every year	Mammogram every 1-2 years
	≥ 50	CBE every year	Mammogram annually

FDA Presentation

- Device Description and Pre-Clinical Data — Kish Chakrabarti, Ph.D
- Algorithm Stability — Nicholas Petrick, Ph.D.
- Clinical Review — Ron Yustein, M.D.
- Statistical Review — Lakshmi Vishnuvajjala, Ph.D.
- Risk/Benefit Analysis — Roselie Bright, Sc.D.

Other FDA Review Team Members

- William Sacks M.D., Clinical
- Harry Bushar, Ph.D., Statistical
- Robert Wagner, Ph.D., Algorithm
- Joseph Jorgens M.S., J.D., Software
- Kevin Hopson, BIMO Inspections
- Fleadia Farrah, GMP Inspections

P050003
T-Scan 2000 ED
Submission and Device Overview

Kish Chakrabarti, Ph.D.
Office of Device Evaluation
August 29, 2006

Device Description/Operation

- Device analyzes multi-frequency capacitance and conductivity values (over all 8x8 sensors in the surface probe) at 17 preset frequencies.
- Results are based on the scan from both breasts.
- Device does not show or identify the location of any suspicious region in either breast.

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Device Description/Operation

The device provides a binary outcome of negative or positive:

- Solid green horizontal line indicates negative
- Hatched red line indicates positive
- Device does not produce any image for diagnosis

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Device Description and Operation of T-Scan 2000 (P970033) approved in 1999

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Intended use of T-Scan 2000 (P970033)

- Adjunct to mammography with equivocal BI-RADS 3, 4 assessments
- Not for cases with clear mammographic or non-mammographic indications for biopsy
- Not a screening device

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Intended use of T-Scan 2000 (P970033)

- Target population ≥ 40 years old
- Attending physicians determine if T-Scan should be used and interpret results

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Device Description/Operation T-Scan 2000 (P970033)

Device :

- Uses a different frequency range
- Uses a different algorithm
- Converts computed capacitance and conductance to gray scale

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Device Description/Operation T-Scan 2000 (P970033)

- Produces an image
- Displays shades of gray
- Provides a bright region on displayed image for malignant tumors compared to its surrounding

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Pre-clinical Data: Proposed Device

- Bench Studies:
  The device complies with the International Electrotechnical Commission standards: IEC 60601-1 and IEC 60601-1-2. The test results and reports are satisfactory.
- Pre-scan Check:
  T-Scan performs pre-scan safety tests each time the device is turned on.
- Software Safety Tests:
  Satisfactory and acceptable

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Pre-clinical Data: Proposed Device

- Biocompatibility and Animal Studies
  Biocompatibility and Animal Studies were assessed for the previous device T-Scan 2000 (P970033) containing the same hand-held surface probe and signal transmitter made of same materials from the same supplier.
- Algorithm Stability Analysis
  Dr. Nick Petrick will discuss this in the following presentation.

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Mirabel P050003
T-Scan 2000 ED
Pre-clinical Studies (cont.)

Nicholas Petrick, Ph.D.
Director, Image Analysis Laboratory
OSEL/CDRH/FDA

Overview

- Algorithm Stability
  - Algorithm architecture and implementation
  - Training and validation datasets
  - Stability analysis

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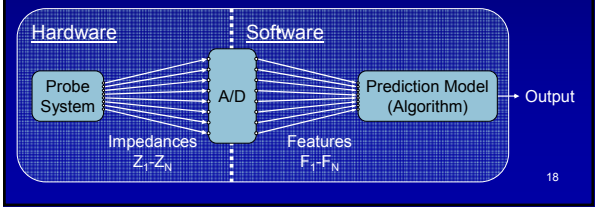
T-Scan Architecture

- Hardware (probe)
- Software (algorithm)
  - Recipe for making decision of suspicious or not
  - Trained using patient data
  - Integral to device operation



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T-Scan Implementation

- Examine patient with T-Scan probe
- Software algorithm
  - Applies classifier
    - Determine score for each breast
  - Applies threshold
    - Determine suspicious or not for each breast
  - Applies logical OR
    - Either breast suspicious → patient suspicious

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Device Architecture

- Impedance measurements
  2 impedance
  17 frequencies
  9 sectors
  306 impedance measurements per breast
- Fairly larger number of initial features

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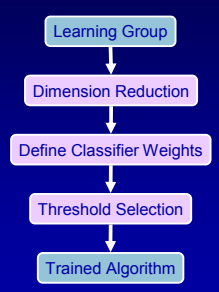
Algorithm Training Process



- Training Data
  - Learning Group
- Dimension reduction
  - 306 measures reduced to 26 blended features
  - Multi-step process
- Determine weights
  - Determine blended-feature weights
- Threshold selection
  - Select cutoff value between suspicious/non-suspicious
- Trained Algorithm
  - Algorithm trained to appropriately score similar patients as in training set

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Stability Analysis

- Algorithm stability
  - Measure of the uncertainty in algorithm performance with variations in test and training data
- Stability of T-Scan related to:
  - Dimension reduction process
  - Estimation of algorithm weights
  - Estimation of cutoff threshold
  - Number and quality of the training case set

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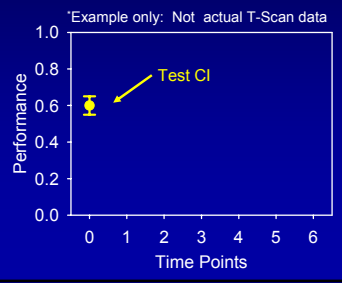
Why stability analysis?

- Indicates if stated performance is due to fortuitous choice of training/test sets



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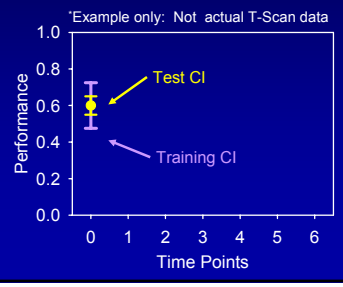

More Stable

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Why stability analysis?

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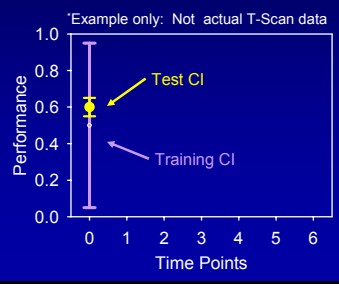

Less Stable

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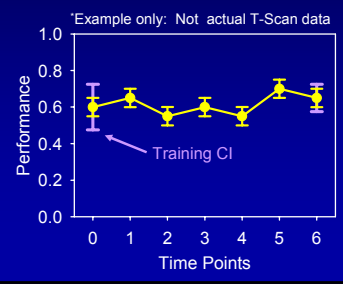
Why stability analysis?

- Algorithms evolve over time as more data is collected
  - T-Scan uses a non-adaptive algorithm
  - Software revisions produce evolving performance estimates



More Stable

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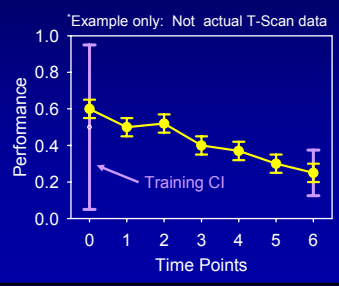

Less Stable

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Developmental and Validation Datasets

Study Group	Cancer Cases	Non-cancer Cases	Patients
Learning	65	754	All yrs
Verification	18	691	≤ 45 yrs
Validation	12	263	≤ 45 yrs
Pivotal Trial	87	1751	≤ 45 yrs

- Learning Group (training)
  - Dimension reduction, algorithm training, threshold determination
- Verification Group
  - Different cases from Learning Group
  - Preliminary verification of performance
- Validation Group
  - Independent cases
  - Validate performance of clinical system
- Pivotal Trial Group
  - Not part of stability analysis

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Bootstrap Stability Analysis

- Bootstrap sampling
  - Sampling with replacement from a sample data set
  - Simple but powerful Monte Carlo method to assess statistical accuracy
- Estimate training variability
  - Bootstrap Learning Group (100 partitions)
    - Apply dimension reduction
    - Estimate classifier weights
    - Estimate cutoff threshold (Sp=0.90)
    - Estimate test performance
      - Verification Group
      - Validation Group
  - Provides estimate of training variability

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Bootstrap Stability Analysis

- Estimate test variability
  - Fix algorithm realization using all training data
    - 26 blended features
    - Fixed blended-feature weights
    - Fixed cutoff threshold
  - Bootstrap Verification & Validation groups (1000 partitions each)
    - Estimate test performance
      - Verification Group
      - Validation Group
  - Provides estimate of test variability

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Bootstrap Stability Analysis

- Table of T-Scan training and test variability

Dataset	Stability Estimate	Specificity			Sensitivity		
		Mean	SD	95% CI	Mean	SD	95% CI
Verification	Training	90%	3%	84-96%†	34%	11%	12-56%†
	Test	93%	2%	89-97%‡	44%	12%	20-68%‡
Validation	Training	87%	4%	79-95%†	29%	13%	3-55%†
	Test	89%	2%	85-93%‡	29%	13%	4-54%‡

†95% confidence intervals calculated by sponsor using bootstrapping
‡95% confidence intervals calculated by FDA using Gaussian assumption

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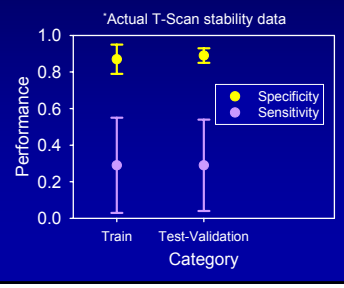
Bootstrap Stability Analysis

- Validation set
  - Training variability roughly on the same order as test variability



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Pre-Clinical Study Comments

- Stability analysis
  - Bootstrap analysis indicates algorithm architecture is not unstable
  - Training variability is not a trivial effect
- Remaining speakers quote only test confidence intervals based on the Pivotal Study data
  - Total variability associated with the algorithm would be somewhat greater than the presented test confidence intervals

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P050003
Mirabel T-Scan 2000 ED

Clinical Review

Ron Yustein, M.D.
Deputy Director, Office of Device Evaluation
August 29, 2006

Reminders about the Device

- ***Not*** **an imaging device**
- ***Not*** **a replacement to any current imaging modalities or techniques to detect/diagnose breast cancer**
- ***Not*** **intended for women with + FHx or CBE**
- **Positive result → further evaluation per M.D.**
- **Intended to be used yearly. Results are for current year – not life-time risk.**
- **Intended to be used by OB/GYNs and PCPs**
- **Will *increase* number of women going on to image screening.**

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Pivotal Clinical Protocols

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Two-Component Pivotal Study

- **Specificity Arm**
  - Age 30-39
  - Negative CBE,
  - Negative FHx
  - *Presumed cancer-free*
  - *No tests to confirm status*
  - Any + T-Scan = FP
  - Any - T-Scan = TN
- **Sensitivity Arm**
  - Age 30 - 45
  - Premenopausal
  - Suspicious lesion on CBE, mammogram, US or MRI
  - Referred for biopsy
  - "Positive" only if histological confirmation
    - Atypical hyperplasia and LCIS = benign

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Two-Component Pivotal Study

- Primary Overall Study Endpoint:
  - "Relative Probability" (RPr)
  - Assess whether a T-Scan + woman is at risk for breast cancer 2 or more times greater than the expected risk in the general target population.

$$RPr = \frac{Se}{(SeRca) + (1-Sp)(1-Rca)} \geq 2.0$$

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FDA Role In Study Design

- Non-Significant Risk (NSR) studies – no formal IDE
- FDA and sponsor held pre-IDE meetings
  - Some concern over estimating Se and Sp from different study populations but FDA accepted that this was a reasonable approach.
  - Acceptable to enrich Se arm due to low prevalence of disease. FDA would request breakdown of study results for 30-39 and 40-45 separately
    - » If $Se_{40-45} < Se_{30-39}$, no major issues.
    - » If $Se_{40-45} > Se_{30-39}$, could present a challenge for modeling results.
  - Demonstration of Relative Probability $\geq$ 2.0 would be clinically meaningful and a reasonable approach.

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Specificity Arm Results

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Specificity Study Results

- Overall Specificity 94.7% (93.7%; 95.7%)
- No statistically significant differences by:
  - CBE Status
  - Hormone Status
  - Menopause Status
  - Family History Status (p=0.08)
- Bra Size

A or B	C or D	> D	Missing
96.8%	93.2%	90.5%	88.2%

$p < 0.05$

- Race

Asian (N=26)	American Indian (N=9)	Caucasian (N=865)	African Amer. (N=51)	Hispanic (N=48)
100%	100%	95.6%	88.2%	87.5%

$p < 0.05$

- Nation

United States	Israel
95.5%	92.7%

$p < 0.05$

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Sensitivity Arm Results

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Sensitivity Arm Baseline Demographics

		Cancer Cases (N=87)	Total (N=390)
Age	30-39	37 (42.5%)	179 (45.9%)
	40-45	50 (57.5%)	211 (54.1%)
CBE	Normal	17 (19.5%)	148 (37.9%)
	Abnormal	70 (80.5%)	242 (62.1%)
Family History	None	68 (84.0%)	316 (82.9%)
	Positive	13 (16.0%)	65 (16.7%)

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Baseline Demographics of Cancer Subjects U.S. versus Israel

		United States	Israel
CBE	Positive	73.1%	83.6%
	Negative	26.9%	16.4%
Family History	Positive	19.2%	14.3%
	Negative	80.8%	85.7%
Hormone Use	Positive	16.7%	14.0%
	Negative	83.3%	86.0%
Bra Size	A or B	40.9%	40.0%
	≥ C	59.1%	60.0%

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Sensitivity Results: Overall and Covariates

		n/N	Se
• Overall		23/87	26.4%
• CBE	Positive	18/70	25.7%
	Negative	5/17	29.4%
• FHx	Positive	4/13	30.8%
	Negative	17/68	25.0%
	Missing Subjects	2/6	33.3%
• Bra Size	A&B	4/26	15.4%
	C&D	8/34	23.5%
	>D	2/3	66.7%
	Missing Subjects	9/24	37.5%
• Hormone Use	Positive	3/9	33.3%
	None	12/57	21.1%
	Missing Subjects	8/20	40.0%

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Sensitivity Results: Race/Ethnicity (FDA)

- Israeli sites did not record race (61/87 cancers)

	Caucasian	African-American	Hispanic	Asian
U.S.	7.7% (1/13)	28.5% (2/7)	0.0% (0/4)	0.0% (0/2)
Israel*	32.8% (20/61)	----------	----------	-------
Total*	28.4% (21/74)	28.5% (2/7)	0.0% (0/4)	0.0% (0/2)

15.4% (2/13)

* Assuming all Israeli patients are Caucasian

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Sensitivity Results: Age and Country (FDA)

	30-39	40-45	All
Overall	18.9% (7/37) (8.0, 35.2%)	32.0% (16/50) (19.5, 46.7%)	26.4% (23/87) (17.6, 37.0%)
U.S.	0.00% (0/11) (0.0, 28.5%)	20.0% (3/15) (4.3, 48.1%)	11.5% (3/26) (2.4%, 30.2%)
Israel	26.9% (7/26) (11.6, 47.8%)	37.1% (13/35) (21.5, 55.1%)	32.8% (20/61) (21.3, 46.0%)

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Sensitivity Results: Intended Population (FDA)

	30-39 year olds who were also CBE Negative and FHx Negative
# (%) Evaluable Cancers	4 of 87 (4.6%)
Sensitivity Overall	25% (1/4)

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Site by Site Variation by Country (FDA)

U.S. Site	n/N	Sensitivity
ARA	0/6	0.00%
BCA	0/1	0.00%
DU	*2/4*	*50.0%*
GWU	0/2	0.00%
KSC	0/4	0.00%
LWH	0/1	0.00%
OSG	*1/2*	*50.0%*
RJG	0/3	0.00%
USC	0/0	------
WR	0/3	0.00%

U.S. Sensitivity = 3/26 = 11.5%

Israeli Site	n/N	Sensitivity
AH	1/10	10.0%
BZ	5/16	31.3%
HH	3/8	37.5%
IBC	1/4	25.0%
It	2/8	25.0%
RAM	8/15	53.3%

Israel Sensitivity = 20/61 = 32.4%

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Sensitivity Arm: Non-Evaluable Cancers

Reason Not Evaluable	Age < 30	Age > 45	Post-Menopause	Prior Chemo	Technical	No TS Result	TOTAL
Number	2	11	7	4	19	1	44
Sensitivity	1/2= 50%	3/11 = 27.3%	1/7 = 14.3%	1/4= 25%	1/19 = 5.3%	NA	7/43 = 16.3%

SENSITIVITY OF *ALL* CASES = (23+7)/(87+44) = 30/131 = 22.9%

NOTE:
- 6 of the 19 Technical cases were patients 30-39.
- 7 post-menopausal women excluded

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"Technical Issues" at U.S. Sites (FDA)

	# Subjects Enrolled	# Enrolled Excluded due to "Technical"	# Cancers in Excluded Population	# Cancers excluded due to "Technical"	T-Scan Results for Excluded Cancers
RFW	37	31	8	7	7 Neg
RJG	56	34	14	12	11 Neg
Total	93	65	22	19 (6 age < 40)	18 Neg

NOTE:
- Technical difficulties: 11.9% (70/590) in Se Arm; only 0.7% in Sp Arm.

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Sensitivity Arm Results
With Post-Menopausal Women

NOTE:
- 7 post-menopausal women age 30-45 with cancer were not included in the prior Sensitivity analyses.

REASONS FOR EXCLUDING THESE SUBJECTS
- Post-menopausal women are at "higher risk" and therefore fall outside the intended use population.
- Post-menopausal women have different breast tissue characteristics.

REASONS FOR INCLUDING THESE SUBJECTS IN AN ANALYSIS
- Original protocol did not specifically exclude post-menopausal women from enrollment and several (24) were enrolled in the Se arm
- Indications for Use sought by sponsor does not specifically exclude them.
- Post-menopausal women were not excluded from the Specificity arm

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Including Post-Menopausal Subjects

- Sensitivity by covariate and country:

		U.S.	Israel	Combined
• Age	30-39	0%	27%	19% (7/37)
	40-45	17%	36%	30% (17/57)
• CBE	Positive	14%	30%	
	Negative	0%	45%	
• FHx	Positive	18%	37%	
	Negative	6%	30%	
• Bra Size	A or B	8%	21%	
	≥ C	8%	38%	
• Menopause	Pre	12%	32%	
• OVERALL		10.3%	32.3%	25.5%

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The Primary Endpoint

Calculation of "Relative Probability"

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Primary Overall Study Endpoint

- Assess whether the probability of having cancer is at least 2 times greater for a T-Scan positive woman than for an average woman in the target population.

$$\text{Relative Probability} = \frac{Se}{(SeRca) + (1-Sp)(1-Rca)} \geq 2.0$$

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Primary Endpoint: Overall Study Population

- All evaluable subjects
  - Sp = 94.7%
  - Se = 26.4%
  - Prevalence (Rca) = 0.15%

Relative Probability = 4.95 (3.16, 7.14)

Note: Primary Endpoint Met

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Primary Endpoint: 30-39 Age Group

- All women 30-39 only
  - Sp = 94.7%
  - Se = 18.9%
  - Prevalence (Rca) = 0.15%

Relative Probability = 3.60 (1.43, 6.19)

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Primary Endpoint: With Post-Menopausal

- Relative Probability = 4.78 (3.23, 7.16)
  - Se 25.5%
  - Sp 94.7%
  - Prevalence 0.15%

NOTE: Primary Endpoint Met

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Primary Endpoint: U.S. versus Israel

	United States	Israel
Without Post-Menopausal Women	Se = 11.5% Sp = 95.5% Rca = 0.15% RPr = 2.55 (0.85, 7.53)	Se = 32.8% Sp = 92.7% Rca = 0.15% RPr = 4.47 (2.78, 7.17)
With Post-Menopausal Women	Se = 10.3% Sp = 95.5% Rca = 0.15% RPr = 2.28 (0.76, 6.81)	Se = 32.3% Sp = 92.7% Rca = 0.15% RPr = 4.40 (2.75, 7.03)

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Primary Endpoint: Race

	Parameters	Relative Probability
Caucasians	Se = 28.4% Sp = 95.6%	6.40
African-Americans	Se = 28.5% Sp = 88.2%	2.41
Hispanics	Se = 0.0% Sp = 87.5%	0.00
Asians	Se = 0.0% Sp = 100%	0.00
American Indians	Se (None) Sp = 100%	N/A

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Effects of Changes in Se, Sp, Rca

- For a given Sp = 94.7%, Rca = 0.15%:

	Overall Relative Probability
Se = 40.0%	7.47
Se = 35.0%	6.55
Se = 30.0%	5.62
Se = 26.4%	**4.95**
Se = 20.0%	3.76
Se = 15.0%	2.82
Se = 10.0%	1.88

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Effects of Changes in Se, Sp, Rca

- For a given Se = 26.4% and Rca = 0.15%

	Overall Relative Probability
Sp = 99.0%	25.4
Sp = 97.0%	8.70
Sp = 94.7%	**4.95**
Sp = 93.0%	3.76
Sp = 90.0%	2.63

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Effects of Changes in Se, Sp, Rca

- For a given Se = 26.4% and Sp = 94.7%

	Overall Relative Probability
Rca = 0.75%	4.84
Rca = 0.45%	4.89
Rca = 0.15%	**4.95**
Rca = 0.05%	4.97
Rca = 0.01%	4.98

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Positive Predictive Value

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Calculation of Positive Predictive Value (PPV)

- Sponsor started with 2 x 2 Matrix of PMA data
  - From both Sp and Se arm
- Noted Prevalence = 87/2141 = 4.1/1000
- Revised table to reflect prevalence of 1.5/1000 by increasing # of non-cancer cases in the Sp arm and maintaining 94.7% TN
- PPV = 23/3134 = 0.00734 = 0.734%
- 1 in 136 T-Scan + patients (1/0.00734) will be cancer positive.
  - Sponsor claims risk in general population 30-39 to be 1 in 667.

NOTE:
1. Prevalence has a large impact on the PPV calculation.
2. Major assumption: Mammography detects 100% of cancers

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Affect of Prevalence on PPV (FDA)

- If table is adjusted to prevalence of 0.05% instead of 0.15% in the same manner.

	Bx -	Bx +	TOTAL
TS -	164653	64	164717
TS +	9260	23	9283
TOTAL	173913	87	174,000

- PPV = 23/9283 = 0.25% = 1 in 400 T-Scan + cases is a cancer.

NOTE: Again, assumes 100% sensitivity for mammography.

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Other Considerations

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Other Considerations

Impact of False Positive T-Scan results

- 1. Mammograms performed as follow-up to FP T-Scan and radiation exposure?
  - 2-views ~ 200-400 mrad.
  - 30 year old can receive 10 additional, normal mammograms before age 40.
  - 2000-4000 mrad over 10 years
- For comparison:
  - Surroundings = 100 mrads/yr
  - Chest x-ray = 5-15 mrad
  - Hip x-ray = 240 mrad
  - Chest CT =1000 mrad
- 2. Impact of positive T-Scan and negative work-up (e.g., mammogram)
  - Was the mammogram misread?
  - Should I have another mammogram?

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Combining U.S. and Israeli Data?

- Sponsor's Rationale for Pooling:
  - No statistically significant difference in patient baseline characteristics
  - No difference in clinical practice
  - No examiner bias (Dichotomous output)
  - No difference in exam quality
  - Israeli physicians were U.S.-trained

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Additional Data

NOTE: Line data from the following references were not available for FDA evaluation and analysis as part of this PMA.

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Stojadinovic et al. *J. Clinical Onc*, 2005

- 1,103 women for screening CBE, imaging or biopsy.
  - 579 subjects at 3 U.S. sites + 524 subjects at 3 Israeli sites
  - 580 subjects under age 40
- Results:

	< 40	Overall
Sensitivity	50% (3/6)	17.4% (5/29)
Specificity	89%	89%
Assumed Prevalence	0.15%	0.6%
Relative Probability	4.52	1.53

NOTE:
- One-arm study
- Se of 50% in subjects < 40 based on only 6 cases.
- Sp = 89% (95% in Sp arm)
- No breakdown of U.S. vs Israel

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Other Stojadinovic Reports

- *Breast Cancer Research and Treatment*, 2005
- 2-Arm Study
  - Sp = 95.1%
  - Se (N=50) 38%
    - 30-39 29%
    - CBE Negative 31%
    - Specificity 81%
  - Pr 7.68 (4.1, 11.3)

NOTE: Se arm study sites correspond to Se study sites in PMA study. Subject overlap with PMA data?

- *U.S. Military Study Annual Report, 2005*
- 1385 women at 5 U.S. military facilities (30-45)
  - CBE followed by TScan.
  - + TScan → Imaging ± Bx
- Se = 33% (1/3)
- Sp = 93%
- Pr = 6.0

NOTE: Cancers or "*high risk lesions*"
Se based on only 3 lesions
? Baseline CBE, FHx status
? 30-39 vs 40-45

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P050003
Mirabel T-Scan 2000 ED Statistical Review

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Outline

- Pivotal Clinical Study
- Specificity Arm with Assumed Normal Cases
- Sensitivity Arm with Benign and Malignant Cases
- Primary Endpoint
- Logistic Regression Estimate of Odds Ratio
- CBE Sensitivity/Specificity
- Conclusions

Pivotal Clinical Study Specificity/Sensitivity Arm Protocols

- Specificity Arm
  - Age 30-39
  - CBE negative
  - No follow-up
  - 15 US and 2 Israeli sites
- Sensitivity Arm
  - Age 30-45
  - Biopsy result
  - 12 US and 6 Israeli sites

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)	25.5% (24/94)
Combined Arms	92.5% (1916/2071)	

Clinical Implications Using the Sponsor's Estimates with Prevalence = 0.0015

- **Se** **26.4% (23/87)**
- **Sp** **94.7% (1658/1751)**
- **Prevalence** **0.0015**

What this means:

- Out of 10,000 women, about 15 are expected to have breast cancer and about 4 of them will be T-Scan positive, while about 11 will be missed.
- Out of the remaining 9,985 women who are expected not to have breast cancer, about 530 of them will be T-Scan positive.

Clinical Implications Using the Sponsor's Estimates with Prevalence = 0.0005

- **Se** **26.4% (23/87)**
- **Sp** **94.7% (1658/1751)**
- **Prevalence** **0.0005**

What this means:

- Out of 10,000 women, 5 are expected to have breast cancer and about 1 of them will be T-Scan positive and 4 will be missed.
- Out of the remaining 9,995 women who are expected not to have breast cancer, about 531 of them will be T-Scan positive.

CBE Status in the two arms

	CBE	Specificity
Sensitivity Arm	Positive	81.8% (148/181)
	Negative	79.1% (110/139)
Specificity Arm	Positive (Not Per-Protocol)	94.9% (56/59)
	Negative	94.7% (1658/1751)

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Baseline Characteristics for Specificity Arm

Characteristic	US	Israel	2-sided p-value
Assumed Normal Cases	1258	493	
Sites	15	2	
Post-menopausal	2.3% (29/1257)	0.6% (3/493)	< 0.02
Hormone Users	39.3% (482/1227)	49.5% (218/440)	< 0.0003
Bra Cup Size ≥ C	54.1% (673/1243)	43.2% (205/474)	< 0.00007
Age (s.d.)	34.6 (2.8)	34.2 (2.9)	< 0.03

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T-Scan Results in Specificity Arm

Characteristic	US Specificity	Israeli Specificity	2-sided Fisher's Exact p-value
Overall	95.5% (1201/1258)	92.7% (457/493)	< 0.03
Pre-menopausal	95.4% (1172/1228)	92.7% (454/490)	< 0.03
Hormone Users	95.9% (462/482)	91.7% (200/218)	< 0.04
Bra Cup Size ≥ C	94.4% (635/673)	88.3% (181/205)	< 0.005
FH Positive	99.2% (126/127)	91.7% (33/36)	< 0.04

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Baseline Characteristics & Results for Sensitivity Arm Benign Cases

(Includes post-menopausal Women)

Characteristic or Result	US	Israel	2-sided Fisher's Exact p-value
Benign Cases	150	170	
Sites	12	6	
CBE Negative proportion	31.3% (47/150)	54.1% (92/170)	< 0.00005
Pre-menopausal proportion	91.3% (137/150)	97.6% (160/164)	< 0.03
Age 30-39 proportion	50.7% (76/150)	42.9% (73/170)	NS
Overall Specificity	82.0% (123/150)	79.4% (135/170)	NS

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Baseline Characteristics & Results for Sensitivity Arm Malignant Cases

(Includes post-menopausal Women)

Characteristic or Result	US	Israel
Malignant Cases	29	65
Sites	10	6
Age 30-39 proportion	37.9% (11/29)	40% (26/65)
Overall Sensitivity	10.3% (3/29)	32.3% (21/65)
FH Negative Sensitivity	5.6% (1/18)	30.0% (12/40)

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Proportion of Cancers for Women Age 30 – 39 Over 4 Subgroups

(Includes post-menopausal Women)

CBE- & FH-	CBE- & FH+	CBE+ & FH-	CBE+ & FH+
11% (4/35)	0% (0/35)	46% (16/35)	43% (15/35)

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T-Scan Sensitivity for Women Age 30-39 in Sensitivity Arm

	CBE- & FH-	CBE- & FH+	CBE+ & FH-	CBE+ & FH+
US Sensitivity	**0% (0/2)**	(0/0)	0% (0/4)	0% (0/5)
Israeli Sensitivity	**50% (1/2)**	(0/0)	17% (2/12)	40% (4/10)
Overall Sensitivity	**25% (1/4)**	(0/0)	13% (2/16)	27% (4/15)

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Sponsor's Primary Endpoint

Sponsor's primary endpoint = "Relative Probability" (RP)

= Se/[(SeRca)+(1-Sp)(1-Rca)], where

Se = Sensitivity, Sp = Specificity, and
Rca = sponsor's breast cancer prevalence = 0.0015.

Note that RP x Rca = Positive Predictive Value (PPV).
RP = PPV/Prevalence

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Sponsor's Primary Endpoint

- Sponsor's success criterion = RP ≥ 2.
- Odds ratio (OR) is the ratio of odds of having a malignancy in the T-Scan positive group to that of the T-scan negative group.
- OR can be shown mathematically to be greater than RP and is used in some statistical analysis performed by FDA.

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Logistic Regression Analysis By FDA

In order to estimate Odds Ratios (OR's) to predict the probability of malignancy for each of the following potentially statistically significant covariables simultaneously, FDA constructed a stepwise binary logit model, using all 2,165 per-protocol women equally weighted from both arms of the study, with benign regarded as normal:

- Menopause (Post- versus Pre-)
- Country (Israel versus US)
- FH (Positive versus None)
- Hormone (No Use versus Use)
- T-Scan (Positive versus Negative)

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Multivariate Overall Logistic Regression Results

Effect by order entered into the logit model	**Estimated Adjusted OR**	**95% CI for OR**
FH (Positive versus Negative)	3.6	(2.1, 5.9)
Country (Israel versus US)	4.0	(2.4, 6.8)
Hormone (Not Used versus Used)	3.3	(1.7, 6.7)
Menopause (Post- versus Pre-)	4.8	(1.7, 11.6)
T-Scan (Positive versus Negative)	2.6	(1.3, 4.7)

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Overall Logistic Regression Conclusions

- Each of (1) being T-Scan Positive, (2) being post-menopausal, or (3) not using hormones has an OR (hence RP) lower bound of the 95% CI for breast cancer < 2.
- Only being in Israel or having a positive FH has a lower bound of the 95% CI for breast cancer risk > 2.
- Controlling for each of the potentially significant covariates is necessary to properly assess the residual effect of T-Scan to predict malignancy.

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Logistic Regression Results for Women Age 30-39

Effect by order entered into the logit model	Estimated Adjusted OR	95% CI
FH (Positive versus Negative)	5.5	(2.6, 11.7)
Country (Israel versus US)	4.4	(2.1, 9.4)
T-Scan (Positive versus Negative)	3.0	(1.1, 8.4)
Hormone (Not Used versus Used)	2.6	(1.0, 6.4)

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Conclusions

- The sponsor's primary endpoint (RP) does not allow for the multitudinous effects of competing covariables, which may statistically influence T-Scan's ability to detect breast cancer. In fact, when the RP is computed for the U.S. and Israel separately, the combined RP is greater than the RP of either country.
- Therefore, the sponsor's RP estimate may be on a different scale, which may not be related to the intended population of CBE- and FH- women age 30-39.
- The separation of Sensitivity and Specificity into 2 arms under different protocols may have unintentionally resulted in 2 populations that are not easy to consolidate.

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Benefit Risk Analysis of T-Scan 2000 ED

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T-Scan Benefit Risk Analysis

FDA and the sponsor agreed that the primary endpoint would be a relative risk of >2.

The sponsor met this endpoint in the unadjusted analysis.

FDA believes that it is also important for the panel to consider the benefits and risks of this device from different perspectives.

This presentation will present alternative analyses for considering the risk/benefit of this device.

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T-Scan Benefit Risk Analysis

Outline

Analysis of sponsor's benefit analysis
- Underlying assumptions
- Calculations
- Discussion

FDA's benefit risk analysis
- Method
- Underlying assumptions
- Calculations
- Discussion

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Sponsor's Benefit Analysis

Underlying assumptions:

- Breast cancer prevalence (FDA verified sponsor's conclusion that prevalence estimates between 0.00017 and 0.0015 do not affect the calculations)
- T-Scan specificity
  - *94.7% overall, per sponsor*
  - *88% for African Americans and Hispanics in Specificity Arm*
- T-Scan sensitivity

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T-Scan Benefit Analysis

Values for T-Scan sensitivity:

- *26.4% used by sponsor, for all women 30-45, CBE+ and CBE-, and both US and Israel.*
- *10.3%, for all US data, including 40-45 year olds and CBE+.*
- *5.6% for all women 30-45 who were FH-, US only.*
- *0% for women 30-39 who were CBE-, US only.*

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T-Scan Benefit Analysis

Sponsor's method: Is rate of cancer detection for T-Scan+ women in indicated group > rate of cancer detected otherwise?

T-Scan sensitivity	Relative probability, T-Scan specificity = 94.6%	Relative probability, T-Scan specificity = 88%*
26.4%	4.9	2.2
10.3%	1.9	0.86
5.6%	1.0	0.47
0%	0	0

* For African Americans and Hispanics in the Specificity Arm.

NOTE: Relative probability of 1 occurs if randomly select women from intended use population.

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T-Scan Benefit Analysis

Logistic regression analysis (presented by the statistician) showed that the following variables are important to consider when doing a benefit analysis:

- Menopausal status
- Country
- Family history
- Hormone use

Note that using T-Scan sensitivity for subgroups only accounted for country and family history.

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T-Scan Benefit Analysis

Another limitation with the sponsor's method:

- The intended use is to screen women
  - and then send T-Scan+ women for screening (film mammography), an *intermediate step, subjecting the ultimate performance of T-Scan to the performance of the intermediate step.*
  - The T-Scan Sensitivity Arm bypassed this step by testing women who were already scheduled for biopsy.

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T-Scan Benefit Risk Analysis

Feig showed the following table of benefits and risks from annual screening mammography of 1 million women age 40-74:

Parameter	Estimate
Lives saved	18,900 women
Possible deaths caused	21.6 deaths
Benefit and risk ratio	875:1
Net benefit in lives	18,878

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T-Scan Benefit Risk Analysis

FDA updated Feig's calculation of deaths caused by using 1.6mSv per view (from Suleiman) and adjusted lifetime risk from 0.00020 for women age 45 to 0.00043 for women age 35.

- 0.000014 deaths per mammographic screen.
- # of deaths depends on # of T-Scan+.

FDA also calculated *cancers detected* rather than *lives saved*.

Cancers detected =
1 million x (presenting prevalence) x (T-Scan sensitivity) x (mammographic sensitivity)

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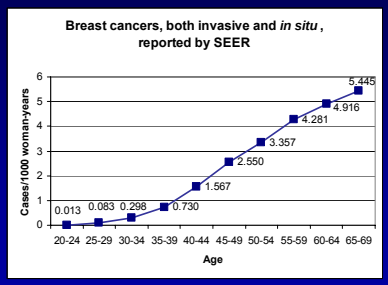
Presenting Prevalence of Breast Cancer

What is the prevalence of breast cancer among women who would present for T-Scan?

First, FDA calculated rate for all women 30-39 from SEER data. Average of prevalence at age 30 and incidence at each following year is 0.058%.



Then calculated rate for women age 30-39, FH-, and CBE-.

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Presenting Prevalence of Breast Cancer

Family History status

Used data from a meta-analysis of 52 studies (CGHFBC)

- Proportion of women age <40 who are FH+ is ~0.04.
- RR cancer among them is ~3.

Clinical Breast Exam status

CBE+ rate found in Bobo study. Higher for age 30-39 than for age 40-49, so because of bias concern, used data for age 40-49: 0.087 were CBE+, with RR of 25.

Also tried: 0.03 are CBE+, with RR of 10 or 3.

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Presenting Prevalence of Breast Cancer

Calculated rates of cancer by FH and CBE status

- in 1 million women,
- assuming that FH+ is not related to CBE+,
- so that there are still 40,000 FH+ women and 960,000 FH- women (next slide).

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Presenting Prevalence of Breast Cancer

FH status	CBE status	CBE rate	# with CBE status	Breast cancer RR for CBE+	Breast cancer rate for subgroup	# of cancers
FH+	CBE+	0.087	3480	25	0.013043	45.39
	CBE-		36,520	1	0.000522	19.05
FH-	CBE+	0.087	83520	25	0.004348	363.13
	CBE-		876,480	1	0.000174	152.43
FH+	CBE+	0.030	1200	3	0.004560	5.47
	CBE-		38,800	1	0.001520	58.97
FH-	CBE+	0.030	28800	3	0.001520	43.77
	CBE-		931,200	1	0.000507	471.78

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Mammography sensitivity for women age 30-39

The best estimates for sensitivity are for women in their 40s:

- Sponsor estimated 70% from literature.
- FDA selected 50% from Pisano for film, age 40-49.
  - -- Digital found many more cancers in that age group, explaining the lower sensitivity estimate for film.

However, sensitivity decreases with younger age.

To be conservative, FDA selected a 5% reduction from 50% to obtain 45% for women age 30-39.

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T-Scan Benefit Risk Analysis (T-Scan 1 million women; app. 53,000 would be sent for mammography due to 94.7% specificity)

Presenting prevalence	T-Scan sensitivity	Possible deaths caused	Mammogram sensitivity			
			70%		45%	
			Cancers found	Cancers found less deaths caused	Cancers found	Cancers found less deaths caused
0.00150	26.4%	0.7	277.2	276.5	178.2	177.5
0.00150	10.3%	0.7	108.2	107.4	69.5	68.8
0.00150	5.6%	0.7	58.8	58.1	37.8	37.1
0.00051	26.4%	0.7	94.2	93.5	60.6	59.8
0.00051	10.3%	0.7	36.8	36.0	23.6	22.9
0.00051	5.6%	0.7	20.0	19.3	12.9	11.1
0.00017	26.4%	0.7	31.4	30.7	20.2	19.5
0.00017	10.3%	0.7	12.3	11.5	7.9	7.1
0.00017	5.6%	0.7	6.7	5.9	4.3	3.5

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T-Scan Benefit Risk Analysis

Population	Scenario	# women to T-Scan	# women to mammogram
Age 30-39, CBE-, FH-	Most favorable (sponsor's) from prior table	3600	190
	Least favorable from prior table	232,600	12,300
Age 30-39, FH+	Mammogram sensitivity = 70%		887
	Mammogram sensitivity = 45%		1379

Sponsor's goal was that T-Scan+ women should have similar probability of cancer as FH+ women.

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T-Scan Benefit Risk Analysis

IF T-Scan sensitivity = 0%:
- *Cause 0.7 deaths*
- *No benefit*

If T-Scan specificity is 94.7%, about 53,000 / 1 million women would have T-Scan+ and mammogram-.

If T-Scan specificity is 88% (found for African Americans and Hispanics in the Specificity Arm), about 120,000 / 1 million women would have T-Scan+ and mammogram-.

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T-Scan Benefit Risk Analysis

The FDA method shows that the relative benefit of T-Scan is highly dependent on several factors in the intended use population:

- *The true specificity of T-Scan (88 to 95%).*
- *The true sensitivity of T-Scan (0 to 26.4%).*
- *The presenting prevalence of breast cancer*, which depends on the:
  - proportion of women and their risk due to CBE+ (poorly known),
  - proportion of women and their risk due to FH+ (well known),
  - dependence of CBE+ on FH+ (unknown).
- *Mammographic sensitivity (uncertain).*

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FDA's Clinical Summary and Issues for Panel Consideration

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Clinical Summary

- Two independent studies used to calculate device Sensitivity and Specificity
  - Se = 26.4% (25.5%)
  - Sp = 94.7%
- Assuming prevalence of 0.15%
  - For overall study population, a relative probability of 4.95 (4.55) with lower bound of 95% CI above 2,
  - Meeting the pre-specified primary endpoint.
- Sponsor concludes that for every 136 positive T-Scan results, 1 will be a cancer case and that this is clinically meaningful compared to the baseline rate of 1 in 667 for the intended age range.

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Issues for Panel Consideration

- Effect of enrichment with subjects > 39, positive CBE, and positive FH on performance in relation to the intended use population and other subgroups?
- Differences in baseline characteristics, Se and Sp results between US and Israel - are the results poolable and applicable to U.S. subjects?
- True Prevalence Rate?
  - 0.15% PPV 1:136
  - 0.05% PPV 1:400
- Risk to health of False Positive results?
- Overall risk/benefit ratio?

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