EXPERT REPORT: ASSESSMENT OF BREAST CANCER RISK IN ASYMPTOMATIC WOMEN AGE 30-39 USING ELECTRICAL IMPEDANCE

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INTRODUCTION

There are approximately 20 million American women between the ages of 30 and 39 (U.S. Census Bureau 2006). In this population, it is expected that conservatively about 1.5 out of every 1,000 women will have breast cancer (Kerlikowske et al. 1993; Kerlikowske et al. 2000; Bobo et al. 2000). While this prevalence rate is lower than breast cancer prevalence in older women, breast cancer in younger women remains a tremendous clinical challenge and is the leading cause of cancer death for women between the ages of 15 and 54 (NCI 2004). In absolute numbers, approximately 12,000 new cases are diagnosed each year in women under age 40 (ACS 2003). In comparison, approximately 9,000 cervical cancer cases are identified each year in the U.S. among all women.

Despite the need for improved breast cancer detection in younger women, annual screening mammography, which has been shown to decrease breast cancer mortality and morbidity in women over age 40, is not recommended to average risk women between the ages of 30-39. This is because the low incidence of breast cancer, combined with a 10-15% lower mammographic sensitivity in women under age 40 does not support routine screening of average risk young women using mammography. Because no screening technology currently addresses the population of women under age 40, Clinical Breast Exam (CBE) is the only modality that is routinely used to screen this population. CBE, however, is limited in this capacity because it is not considered sensitive for small lesions, is highly dependent upon the examiner, and is difficult to compare from year to year. Accordingly, studies show that most women under 40 detect their own cancers, with self-detected cancers occurring at a relatively advanced stage (Park et al. 2000; Zabiki et al. 2006). In general, delayed detection leads to more aggressive and costly treatment regimens as well as greater morbidity and lower survival rates (Kroenke et al. 2004; Tabár et al. 1999).

Mammography screening is offered to women under the age of 40 if they have known familial, genetic, or personal risk factors. But, it should be recognized that the vast majority of women who develop breast cancer (90%) do not have one of these known risk factors, and thus they are generally screened with clinical and/or self breast exam only (Pharoah et al. 2000; Hall et al. 2001; Verkooijen et al. 2006).

Because the reliance upon known risk factors as a criterion for additional screening fails to identify most women who develop breast cancer, we are keenly interested in technologies that can help identify an additional cohort of young women who are at elevated risk for the disease. The use of risk assessment methods can identify elevated breast cancer risk in women who otherwise would be overlooked by the current Standard of Care, but who are likely to benefit from additional surveillance or imaging.

THE T-SCAN ED AS A RISK ASSESSMENT TOOL, NOT A DIAGNOSTIC TOOL

The T-Scan™ 2000ED (T-Scan ED) is used to assess breast cancer risk in women under the age of 40 through the measurement of electrical impedance variables across the breast and the identification of impedance patterns which are associated with an increased risk for breast cancer. This information can be used to support the consideration of additional surveillance or imaging studies such as mammography, ultrasound, or MRI for women who would otherwise be screened only with CBE.

The T-Scan ED exam is similar to other risk assessment studies in the Ob/Gyn setting. The Down Syndrome risk screening model offered in the first trimester of pregnancy, for example, relies upon measures of nuchal translucency and two blood serum markers (PAPP-A and ßhCG) to assess the risk for Down Syndrome, a form of fetal aneuploidy. Women under the age of 35, who typically would not be offered diagnostic testing with amniocentesis or chorionic villus sampling (CVS), are encouraged to do so when risk assessment studies indicate that they are at a level of risk which is consistent with women older than 35, and therefore require additional, definitive studies.

Similar to the T-Scan ED model, the prenatal screening paradigm for Down Syndrome offers women a means for individual risk assessment so that younger women with an elevated risk of disease are identified and encouraged to consider additional confirmatory testing. In both examples, the judicious use of a non-invasive and low-cost risk stratification tool provides us with an opportunity to identify women who otherwise would be excluded from further testing and could suffer significant consequences.

In evaluating the T-Scan ED pivotal study and indication for use, we found it important to remind ourselves that the T-Scan ED exam, like BRCA testing, does not detect cancer. The exam can only be used to identify young, asymptomatic women who are likely to benefit from additional screening. It cannot be used to screen women over age 40 (the device automatically suggests that women over 40 undergo annual mammography as per the Standard of Care). The device cannot be used to "rule out" an existing symptom (if CBE results, which must be entered into the system prior to performing an exam, are abnormal, the system recommends additional imaging irrespective of the T-Scan ED result) and the device cannot be used to localize a finding (the exam is either negative or positive) and no image of the breast is rendered.

We also note that there is a clear distinction between risk assessment tools as compared to imaging or other procedures for the purpose of detecting cancers (or other abnormalities) in individual women. This distinction is critical for understanding and interpreting the pivotal trial and performance characteristics of the T-Scan ED. Specifically, a risk assessment tool provides a measure of individual risk by taking into account the overall disease prevalence in a target population combined with the known performance characteristics of the test in terms of sensitivity and specificity. For risk assessment tools, a high degree of specificity (a low number of false negatives) is of primary interest for the method to be valuable for routine use. Diagnostic methods, on the other hand, are intended for use in patients who are known to have a risk or a symptom, and require a specific diagnosis. Therefore, diagnostic studies must be sensitive enough to offer a reasonable assurance of health or disease to patients who are referred for diagnostic testing. Risk assessment tools are, by definition, designed to screen large populations and identify various levels of risk, generally on a statistical basis. They are not designed to be, or to replace, diagnostic methodologies.

EVOLUTION OF T-SCAN TECHNOLOGY

In April 1999, the U.S. Food and Drug Administration (FDA) approved Mirabel's first system, the TS 2000 and FDA identified the device as a "major medical device breakthrough" in their annual report. However, while the initial approval substantiated the association between electrical impedance scanning (EIS) and breast cancer detection, the first device was positioned to avoid unnecessary biopsies in women having equivocal mammograms; it was not designed as a pre-screening tool to assess breast cancer risk in otherwise healthy women. Since the original FDA approval, Mirabel has refined the technology to address the unmet clinical need discussed above, namely, to focus on the development of algorithms which serve not to diagnose breast cancer, but to yield an absolute risk for breast cancer in 30-39 year old women that is consistent with, or higher than, the average absolute risk in women age 40-49. The level of risk for 40-49 year olds is considered sufficient under the current Standard of Care to justify screening mammography.

PIVOTAL TRIAL RESULTS

In order to quantify the relative and absolute risk of breast cancer in women who are tested with the T-Scan ED system in the target population, a pivotal multi-center clinical trial in the U.S. and Israel was developed with input from the FDA. The study included two separate arms: one arm estimated device specificity in a cohort of 1751 healthy women aged 30-39, and the second arm measured T-Scan ED performance in a cohort of 390 women who were scheduled for biopsy, 87 of whom had cancer, and 303 of whom had benign lesions. The 390 women in the sensitivity arm were scheduled for biopsy based on earlier findings and ranged in age from 30-45. This expanded age range for the evaluation of sensitivity of the T-Scan ED was accepted by the FDA as an appropriate

means to allow more expeditious accrual of women while maintaining breast tissue characteristics that are consistent with the target age range.

We reviewed the decision to include of women between 40-45 years of age in the sensitivity arm (also referred to as an “enriched” population) and agree that this was a clinically reasonable means for enhancing the number of breast cancers in the study. We note that initiation of screening mammography at age 40 is not related to any specific change in breast tissue due to age, and that alterations in breast tissue are associated with hormonal changes at or around the time of menopause. We therefore agree that it is acceptable to include women up to age 45 in the sensitivity arm of the study so long as postmenopausal women, who undergo hormonal changes that may affect breast tissue, are excluded from the analysis irrespective of age.

The primary endpoint and success criterion determined with the FDA prior to study initiation entailed using estimates of sensitivity, specificity, and the prevalence of breast cancer in the target population to calculate the probability that a woman who is T-Scan ED positive has breast cancer relative to a randomly selected woman from the target population. A conservative estimate of the prevalence of cancer in the target population based on the literature is 1.5 cancers per 1,000 women or 1 cancer per 666 women. Prior to the initiation of the pivotal trial, it was agreed with FDA that a clinically relevant threshold for success of the T-Scan ED device would be a relative probability for breast cancer that is equal to or greater than two (2) times the average risk in the target population, which corresponds to the risk of developing breast cancer in a woman with a first degree relative with breast cancer.

The pivotal study results showed a specificity of 94.7% and a sensitivity of 26.4%. This translates to a relative probability for breast cancer of 4.95 in T-Scan ED positive women. These results are well in excess of the success criterion of 2.

Table 1 provides a comparison of the primary endpoint for the T-Scan ED trial in comparison to other relevant measures of breast cancer risk.

Table 1

Relative and absolute risk for breast cancer compared to study threshold and baseline patient populations

Patient Population	**Relative Risk for Breast Cancer (95% CI)**	**Absolute Risk for Breast Cancer**	
T-Scan ED Pivotal Study Results, Amended (87 cancers, 1751 benign): T-Scan ED Positive Risk	**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	1:344 = (1/400) x 0.85=340	0.0029

By yielding a specificity rate of 94.7%, it is expected that 5.3% of women who are tested with the T-Scan ED device will have positive exam results. By identifying approximately 26% of cancers, the T-Scan ED essentially divides asymptomatic women of average risk into two groups, the T-Scan ED positive cohort which includes 5.3% of all women and 26% of all cancers and a T-Scan ED negative group which includes 94.7% of women and 74% of cancers.

Additionally, there were no reported cardiac, neurological, dermal, thermal, or allergic reactions or adverse events, nor any reports of patient discomfort. This outcome echoed similar findings in the pilot study and in more than 10,000 prior examinations with the predecessor TS 2000 device.

BREAST CANCER YIELD IN T-SCAN ED POSITIVE POPULATION

Another manner of viewing the pivotal study results is to compare the expected yield of cancers per mammogram once women between the ages of 30-39 test positive on the exam and are referred to mammography or another imaging modality. In this case, we used mammography as the gold standard because it is the most widely utilized means for breast cancer detection.

To estimate the theoretical yield of cancers per mammogram performed in T-Scan ED positive women, we took into account that the sensitivity of mammography is expected to be lower in 30-39 year old women than in women 40-49. Estimates of the sensitivity of

mammography for women in their 30's vary considerably (70-89%) among mammographic screening trials (Foxcroft et al. 2004; Jeffries and Adler 1990; Kerlikowske et al. 2000; Shaw de Parades et al. 1990). We agree that a 70% sensitivity is an appropriately conservative estimate, as used by Mirabel in the PMA submission. Thus, to discover 1 cancer in the cohort of T-Scan ED positive women, it would be expected that 194 mammograms would be performed (incidence of 1 cancer per 136 women, detection rate with mammography 70%, yields 194 mammograms per cancer detected). This cancer yield is about twice as high as the routine and widely accepted cancer detection rate in women between the ages of 40-49 which is approximately 1 cancer per 400 mammograms.

As stated above, approximately 400 mammograms are currently performed to detect each cancer in women aged 40-49. If the sensitivity of mammography in this age group is 85% (Livner 1997), the estimated prevalence of cancer in women 40-49 is 0.0029. The estimated prevalence of breast cancer in the T-Scan high risk group based on the results of the pivotal trial (i.e., T-Scan positive) is 0.0073 (or 1 cancer in 136 women), more than twice as high as that in women in their 40's (0.0029). Thus, by concentrating approximately 26% of cancers into a cohort including only 5.3% of women, the device yields a sub-population of women who are now recognized to be at a level of risk which justifies further screening with mammography, ultrasound, or other means. While the estimated prevalence in T-Scan ED positive women is 1 cancer in 136 women (0.0073), in average risk women the risk is approximately 1 cancer in 666 women (0.0015) (Kerlikowske et al. 1993), and the prevalence is approximately 1 in 900 in women who test negative on the exam.

COMMENT ON APPARENT DIFFERENCES IN SENSITIVITY BETWEEN ISRAEL AND U.S.

In reviewing the data from the sensitivity arm of the pivotal trial, we noted that the point estimate of device sensitivity in Israeli clinical sites was higher than the sensitivity in U.S. sites. While this regional analysis was not part of the study design, the apparent difference in sensitivity between the two countries was initially of interest to us. To evaluate if the sensitivity gap was associated with differences between the study populations in Israel and the U.S., a careful analysis of all covariates which impacted sensitivity in the pivotal trial was conducted. The analyses showed that all factors measured at the baseline in the sensitivity cohort and potentially associated with device sensitivity were consistent across both locations, and therefore there is no statistical justification for not pooling the data between sites in the U.S. and those in Israel. Any observed numerical differences may be due to expected variability with small sample sizes.

A report provided by Dr. Stojadinovic regarding the interim results of an on-going U.S. Army-funded, multi-center study using the T-Scan ED device in an ethnically diverse population of young women in the U.S. indicates that the sensitivity at high enrolling U.S. sites is virtually identical to the sensitivity reported from Israeli sites (Stojadinovic

2005). The interim results also report that a T-Scan ED positive woman is 6 times more likely to have a pre-malignant or malignant lesion than a T-Scan ED negative woman.

CONCLUSIONS

As physicians and professionals with an expertise in women's health, epidemiology, and statistics, we have carefully considered the T-Scan ED breast cancer screening paradigm, the design and execution of the pivotal study, issues raised by FDA, and the manner in which this instrument is likely to be incorporated within the context of the Standard of Care for breast cancer risk assessment in young women.

Because all candidates for the T-Scan ED exam are asymptomatic, under the age of 40, and have no known risk factors, it is imperative to recognize that these women would not be identified as having increased risk without the availability of the T-Scan ED exam, and typically would not be referred to a radiologist until the age of 40 or the detection of a palpable mass.

Given that the T-Scan ED exam provides useful information, does not entail risk to the patient and fills an important clinical void for both patients and physicians, we fully expect that as the T-Scan ED comes to market it will occupy an important place in the Ob/Gyn risk assessment armamentarium and drive further development in an area that is very much in need of technological improvement.

We believe that sufficient data has been presented to conclude the T-Scan ED device is both safe and effective, and can be used as a complement to CBE in asymptomatic women ages 30-39. The pivotal trial data strongly support the conclusion that the T-Scan ED exam can successfully partition women into two groups: one that has an elevated risk for cancer and would benefit from additional surveillance and one that has an average (or lower) risk who would follow the current Standard of Care.

The T-Scan 2000 ED system addresses an unmet clinical and public health need, and presents no notable risks to the patient. We believe this PMA meets the standard for establishing safety and effectiveness, and therefore support approval of this technology for the proposed indications as labeled.

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REFERENCES CITED

American Cancer Society (ACS). 2003. Breast Cancer Facts & Figures 2003-2004.

Bobo JK, Lee NC, Thames SF. 2000. Findings from 752081 clinical breast examinations reported to a national screening program from 1995 through 1998. *Journal of the National Cancer Institute* 92:971-976.

Foxcroft LM, Evans EB, Porter AJ. 2004. The diagnosis of breast cancer in women younger than 40. *The Breast* 13:297-306.

Hall IJ, Burke W, Coughlin S, Lee NC. 2001. Population based estimates of family history or breast cancer among women. *Community Genetics* 4:134-142.

Jefferies DO, Adler DD. 1990. Mammographic detection of breast cancer in women under the age of 35. *Investigative Radiology* 1:67-71.

Kerlikowske K, Carney PA, Geller B, Mandelson MT, Teplin SH, Malvin K, Ernster V, Urban N, Cutter G, Rosenberg R, Ballard-Barbash R. 2000. Performance of screening mammography among women with and without a first-degree relative with breast cancer. *Annals of Internal Medicine* 133:856-863.

Kerlikowske K, Grady D, Barclay J, Sickles EA, Ernster V. 1993. Positive predictive value of screening mammography by age and family history of breast cancer. *Journal of the American Medical Association* 270:2444-2450.

Kroenke CH, Rosner B, Chen WY, Kawachi I, Colditz GA, Holmes MD. 2004. Functional impact of breast cancer by age at diagnosis. *Journal of Clinical Oncology* 22: 1849-1856.

Livner M. 1997. The medical audit; statistical basis of clinical outcomes analysis. In, *Diagnosis of Diseases of the Breast*. Bassett LW, Jackson VP, Jahan R, Fu YS, Gold RH, eds. WB Saunders, 127-140.

National Cancer Institute (NCI). 2004. Fact Book.

Park BW, Kim SI, Kim MH, Kim EK, Park SH, Lee KS. 2000. Clinical breast examination for screening of asymptomatic women: The importance of clinical breast examination for breast cancer detection. *Yonsei Medical Journal* 41:312-318.

Pharoah PD, Lipscombe JM, Redman KL, Day NE, Easton DF, Ponder BA. 2000. Familial predisposition to breast cancer in a British population. *European Journal of Cancer* 36:773-779.

Shaw de Parades E, Marsteller LP, Eden BV. 1990. Breast cancers in women age 35 and younger: mammographic findings. *Radiology* 177:117-199.

Stojadinovic A. 2005. Department of Defense, Annual Report: Electrical Impedance Scanning (EIS) for the Early Detection of Breast Cancer in Young Women.

Tabár L, Duffy SW, Vitak B, Chen HH, Prevost TC. 1999. The natural history of breast carcinoma: What have we learned from screening? *Cancer* 86:449–462.

U.S. Census Bureau, Population Division. 2006. Table 1: Annual Estimates of the Population by Sex and Five-Year Age Groups for the United States: April 1, 2000 to July 1, 2005 (NC-EST2005-01). May 10, 2006.

Verkooijen HM, Chappuis PO, Rapiti E, Vlastos G, Fioretta G, Sarp S, Sappino AP, Schubert H, Bouchardy C. 2006. Impact of familial risk factors on management and survival of early-onset breast cancer: a population-based study. *British Journal of Cancer* 94:231-238.

Zabicki K, Colbert JA, Dominguez FJ, Gadd MA,Hughes KS, Jones JL, Specht MC, Michaelson JS, Smith BL. 2006. Breast cancer diagnosis in women </= 40 versus 50 to 60 years: Increasing size and stage disparity compared with older women over time. *Annals of Surgical Oncology* (online ahead of print).