

FDA Panel Rejects Breast Cancer Screening Device

BY JOHN R. BELL
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GAITHERSBURG, MD. — A device intended for use in the annual breast cancer screening of women aged 30-39 years who have no family history of the disease and a negative clinical breast examination was found not effective in a unanimous vote by the Food and Drug Administration Obstetrics and Gynecology Devices Panel in August.

The T-Scan 2000ED is manufactured by Mirabel Medical Systems and uses a 1-volt electrical current to collect 306 measures of impedance for each breast. Mirabel believes differences in impedance can indicate the presence of cancer; women with positive results would then be referred for mammography or ultrasound. A positive T-Scan result is shown on the operator's monitor as a red line, and a negative result appears as a green line; no tissue imaging is produced.

A principal objection of the panel was that the sensitivity arm of the study included women aged 30-45 years, rather than just the 30-39 target age group included in the specificity arm. Moreover, both arms included clinical sites in Israel, where the population is dissimilar to that of the United States in ethnic makeup, body mass index, and possibly brassiere cup size and other factors, panel members noted.

The racial composition of both study arms also raised concerns; minority patients were underrepresented in comparison with the U.S. population, several panel members noted. In the specificity arm, 1.5% of the patients were of Asian descent, 2.9% were black, and 2.7% were Hispanic. In the sensitivity arm, 2.3% were Asian, 8% were black, and 4.6% were Hispanic.

The prospect of needlessly alarming patients with positive T-Scan results later belied by negative mammograms was raised by the panel. The FDA deduced from Mirabel's data that using a prevalence of 0.0015 in a population of 10,000 women, 530 would receive false positives. At the same time, T-Scan would identify

4 of 15 expected cancers in the group and miss roughly 11 cancers. Some panel members worried that false positives would lead to increased patient anxiety that might not be assuaged by negative mammogram testing. Specificity was calculated at 94.7.

Dr. Mark Akin, a private-practice gynecologist in Austin, Tex., and one of several physicians to use the device in clinical trials, believes any extra anxiety is minimal and worth the potential benefit. "What-

ever level of anxiety [my patients] may have had, I'm certain that it pales in comparison with the devastation a woman in her 30s experiences when she is told she has advanced breast cancer and will never see her children grow up. What I saw in my study were young women who were grateful that I cared enough to test a new device in order to potentially find breast cancer when it was early enough to have a chance at cure," he said in an interview. "Although the pooled data had a 95% specificity, out of my patients, I only had six positive findings. Statistically, [that] should have been 18. These T-Scan-positive patients were told they had a 99% chance of being normal. All six subsequently had a screening mammogram that was normal. I did not observe any more anxiety in these patients than when a patient has an abnormal Pap smear and goes on to have a normal colposcopy.

Also of concern to some panel members was the predetermined requirement of 2 for relative probability, meaning that any woman in the target age range with a positive T-Scan finding would need to be twice as likely to have breast cancer as the average woman in the 30- to 39-year-old population. Relative probability was ultimately determined to be 3.6. However, at least one panel member regarded the threshold of 2 as inappropriate. "I think

the 2 hurdle is much too low. ... It absolutely must be associated with age. A 30-year-old is incredibly different from a 39-year-old in terms of risk for breast cancer," said Donald Berry, Ph.D., chairman of biostatistics and applied mathematics and director of cancer research at the University of Texas M.D. Anderson Cancer Center, Houston.

According to the FDA's analysis of the sensitivity trial, there were four confirmed cancers in women aged 30-39 who had neg-

ative clinical breast examination findings and negative family history of cancer. Two cases were in the United States, and two were in Israel, where one was detected by the T-Scan. An additional 11 cancers were confirmed in the 40-45

age group, of which 4 were detected by T-Scan. Thus the device detected 5 of 15 overall cancers and 1 of 4 cancers in women younger than 40, for a sensitivity rate of 25%, the FDA concluded.

"We have, at the maximum, 15 cancers and 5 assessments by T-Scan; this would establish a new low for the FDA in terms of level of evidence," Dr. Berry said before the 10-0 vote.

Dr. Akin disagreed. He explained in an interview, "The T-Scan identifies 5% of the population that has a fivefold greater chance of breast cancer than the rest of the population. ... Since mammogram screening starts at age 40 for the general population (solely based upon the age at which their risk exceeds 1 in 300-400), it makes sense to screen younger T-Scan-positive patients, whose risk is three times higher than [that of] a 40-year-old," he said.

Other gynecologists also spoke in favor of approval in the public comments forum at the meeting. Dr. Steven Goldstein, professor of ob.gyn. at New York University, noted that whereas 12,000 women aged 30-39 are diagnosed with breast cancer each year, only 9,000 women total are diagnosed

with cervical cancer annually. "For all the talk these days about HPV and vaccines, the cervical cancer success story is really the result of screening—the Pap smear." Moreover, "Clinical use allows maturation and further refinement of virtually all medical technology, and I'm confident the same would be true of electrical impedance, if given the chance," he added.

No panelists had concerns regarding the safety of the device. A previous version, the T-Scan 2000, was deemed safe and effective by the FDA in 1999 for clarification of equivocal mammographic findings.

Dr. Ron Ginor, the CEO of Mirabel, noted that an ongoing trial of a larger and more diverse population of women in the U.S. military is underway. "The bottom line is this: ... We have to figure out how we're going to take the appropriate leap of faith or not take a leap of faith and remain with no technology," Dr. Ginor said.

Dr. Akin echoed this sentiment. "Unfortunately, women aged 30-39 in the U.S. currently find their own breast cancers 71 percent of the time, frequently when the tumor is at an advanced stage and treatment is no longer going to prevent high morbidity or death."

Dr. Berry, however, believes that even in 39-year-olds, breast cancer is too rare and the device's sensitivity too low to justify its approval. "Among 1,000 39-year-olds flagged by the T-Scan, 5 would have cancer," he said in an interview. "About three times as many women (15) among the 19,000 that are not flagged would have undetected cancer. ... We don't know that the 5 women identified as having cancers would actually benefit, but we know that 995 women without cancers will experience a variety of negative effects, from anxiety because of their positive test result to biopsies.

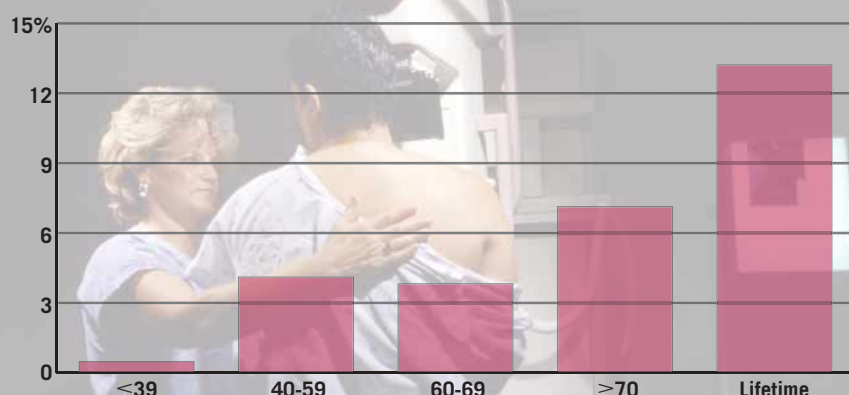
"There's a reason mammography is not recommended for women in their 30s: The disease is so rare that the negatives clearly outweigh the positives," Dr. Berry said.

The FDA usually follows the recommendations of its advisory panels. ■

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DATA WATCH

Probability of Developing Invasive Breast Cancer, by Age



Notes: For those free of cancer at beginning of age interval. Based on cancer cases diagnosed during 2000-2002.
Sources: National Cancer Institute, American Cancer Society

Four Gene Profiles Predict Similar Ca Outcomes

Four of five different models for profiling gene expression in breast cancers produced concordant results, showing significant agreement in predicting disease outcome even though they tested for evidence of different genes.

Researchers used samples from breast cancers excised from 295 women to compare the results of five different gene-expression profiling studies. The studies assess whether given genes are expressed in the tumors, which enables clinicians to more accurately estimate the tumor's aggressiveness, wrote Dr. Cheng Fan of the University of North Carolina, Chapel Hill, and associates (N. Engl. J. Med. 2006 355:560-9).

The first model uses gene-expression profiles to identify the cancer's subtype, differentiating between tumors that originate from luminal cells or basal cells and determining if the tumor is human epidermal growth factor receptor (HER)-2 positive.

The second model identifies the levels of expression of 70 genes thought to regulate the cell cycle, invasion, metastasis, and angiogenesis. The third model calculates the likelihood of cancer recurrence in estrogen receptor (ER)-positive, node-negative tumors by assessing their expression of 21 genes. The fourth model assesses the expression of wound-response genes, which identifies tumors that are more likely to metastasize because they have activated pathways for matrix remodeling, cell motility, and angiogenesis.

All four of these models were significant predictors of relapse-free survival and overall survival.

The fifth model uses a ratio of the levels of expression of two genes: one encodes homeobox 13; the other encodes the interleukin-17B receptor. This model was not predictive of survival.

—Mary Ann Moon