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FDA Approves Genetic Test for Patients With Breast Cancer

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Medscape Medical News 2008. © 2008 Medscape

July 22, 2008 — The US Food and Drug Administration (FDA) has approved the genetics-based *SPOT-Light* test (Invitrogen Corp) to help predict response to trastuzumab (*Herceptin*, Genentech) therapy in patients with breast cancer when used in conjunction with other clinical information and laboratory test results.

"This test is used to determine which patients will receive herceptin therapy," Steven Gutman, MD, FDA director, Office of In Vitro Diagnostics, told *Medscape Pathology & Lab Medicine*. "As is true with all tests, there can be false-positive or -negative results."

Fernando Schmitt, MD, PhD, professor of pathology and director of pathology and senior research at the Institute of Pathology and Molecular Immunology of Porto University in Portugal, provided independent commentary for *Medscape Pathology & Lab Medicine*.

"The potential benefits of any test that assesses [human epidermal growth factor receptor 2 (HER2) include] selecting patients that can respond to a specific therapy," Dr. Schmitt said. "In the case of HER2, besides trastuzumab, some specific responses to chemotherapy, like regimens with anthracyclines, are also important."

The new HER2 chromogenic in situ hybridization (CISH) test measures the number of copies of the HER2 gene, which regulates the growth, division, and repair of cancer cells, in tumor tissue. Although normal breast cells have 2 copies of the HER2 gene, breast cancer cells may have more copies of the HER2 gene. Overexpression of HER2 protein results in greater stimulation of breast cancer cells, causing them to replicate more quickly.

Using an appropriately stained biopsy specimen, the new test allows visualization with a standard light microscope of a color change that identifies HER2 genes, thereby eliminating the need for fluorescent microscopy. Another advantage of the test when compared with existing assays is its ability to store the tissue for future analysis.

"There is a wrong idea that [the] SPOT-Light test is easier to do and interpret than the [fluorescence in situ hybridization (FISH)] testing, [but] it is not true," Dr. Schmitt cautioned. "Both need a pathologist with experience in the field and must be done with rigorous quality control. Therefore, there could be harm to testing for HER2 using SPOT-Light technology if we think that this technology is easier than FISH."

Patients identified with the new test as overexpressing HER2 protein can be treated with the monoclonal antibody trastuzumab, which targets HER2 protein production and helps suppress growth of HER2-positive cancer cells.

"The use of CISH techniques in routine pathology of breast cancer cases to assess HER2 gene copy number will be as important as FISH techniques to select patients with HER2 amplification for specific treatment with trastuzumab," Dr. Schmitt said. "Since this drug is approved for adjuvant therapy, the SPOT-Light test could be used or to study 2+ positive cases by immunohistochemistry or even in all primary cases of breast carcinoma."

The pivotal trial for FDA approval of the new test used breast tumor samples from patients in the United States and Finland and confirmed efficacy in identifying the number of HER2 genes. However, sensitivity, specificity, and predictive values of SPOT-Light have not been determined with regard to determining likelihood of response to trastuzumab, according to Dr. Gutman.

"A surrogate measurement was used comparing this test to standard immunohistochemical testing," Dr. Gutman said. "Positive agreement was 84.2%, negative agreement was 97.6%, and total percentage agreement was 95.1%."

Dr. Schmitt explained that if response to therapy were to be considered a gold standard, then the ideal test for HER2 would approach 100% sensitivity and 100% specificity. However, accurate determination of HER2 status should not be viewed exclusively in terms of benefit from anti-HER2 therapy.

"Patients with breast cancers that overexpress HER2 differ greatly in their response to trastuzumab," Dr. Schmitt concluded. "Available clinical data indicate the near certainty that there are patients who truly overexpress HER2 but have upstream or downstream anomalies (PTEN deficiency, overexpression of insulin-like growth factor receptor, among others) that render the interaction with trastuzumab ineffective, and it would not be appropriate to consider these patients as having HER2-negative disease.... The SPOT-Light test will have a great impact in public health, because it will help to identify the 20% of breast cancer cases that have HER2 amplification and therefore can benefit from specific therapy."

Dr. Gutman and Dr. Schmitt have disclosed no relevant financial relationships.

FDA Medwatch 2008.
