False negative results found in prognostic testing for breast cancer

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A recent study evaluating HER2 testing in a large cohort of women with breast cancer found important limitations in the conventional way HER2 testing is performed in the US and internationally.

Dartmouth-Hitchcock Norris Cotton Cancer Center physicians and researchers retested tumor samples from a large group of women and

found that 22 out of 530 women had their tumor type incorrectly classified. They reported their findings in a publication titled "Assessing the Discordance Rate between Local and Central HER2 Testing in Women with Locally Determined HER2-Negative Breast Cancer," which was published in *Cancer* on June 13, 2014.

Breast cancer is categorized into several subtypes based on conventional laboratory, and newer molecular tests. This study looked at the accuracy in classifying breast cancers in one particular subtype, specifically those that are "human epidermal growth factor receptor 2" or HER2 positive. What is particularly important in accurately determining HER2 in breast cancer is that when a woman's cancer tests positive for HER2, there are specific treatments proven extremely effective in improving outcome and preventing recurrence of cancer. These HER2 directed, or targeted, therapies are critically important in treating women with HER2 positive breast cancer.

"We, and other groups, have previously shown that a certain percentage of cases found to be HER2 positive in local laboratories are in fact HER2 negative when tested in more experienced central labs. There has, however, been almost no research evaluating the accuracy of a negative HER2 result," said Peter A. Kaufman, MD. "This is the first large study to look at this. What is comforting is that we found that re-testing in experienced larger labs confirmed the original local lab results in the majority of cases."

Kaufman noted that they did find about four percent of cases that were originally determined to be HER2 negative were in fact HER2 positive on repeat testing. Many of these cases were detected as being positive by testing for HER2 using both of two different and complementary tests (IHC and FISH, as described below).

The repercussions of incorrectly identifying a cancer's subtype are

considerable. "While it is comforting that only four percent of these women were misclassified initially, this is an enormous issue for those who fall into this group," said Kaufman. "This is because HER2 targeted therapies are critically important for women with HER2 positive breast cancer."

The variance in accuracy may be related to how tests are conducted in smaller versus larger pathology laboratories. Two different tests are approved for and widely used for HER2: immunohistochemistry (IHC) or florescence in situ hybridization (FISH). Either test may be used to determine a woman's HER2 status. Frequently, based on recommendations by leading oncology groups, one or the other is used. In this case, using both tests allowed researchers to uncover errors resulting from reliance on a single test. Of the 22 samples incorrectly categorized, 18 had been processed by a local laboratory using only one testing method.

The analysis was based on the VIRGO study, a large, disease-based, observational cohort study of more than 1,200 women with HER2-negative metastatic breast cancer from June 2008 through January 2011. Out of the 1,267 patients enrolled in VIRGO, 776 submitted samples for this study from which 552 were suitable for centralized testing using IHC and FISH assays.

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