Updated testing guidelines make more women eligible for herceptin, yet benefit uncertain

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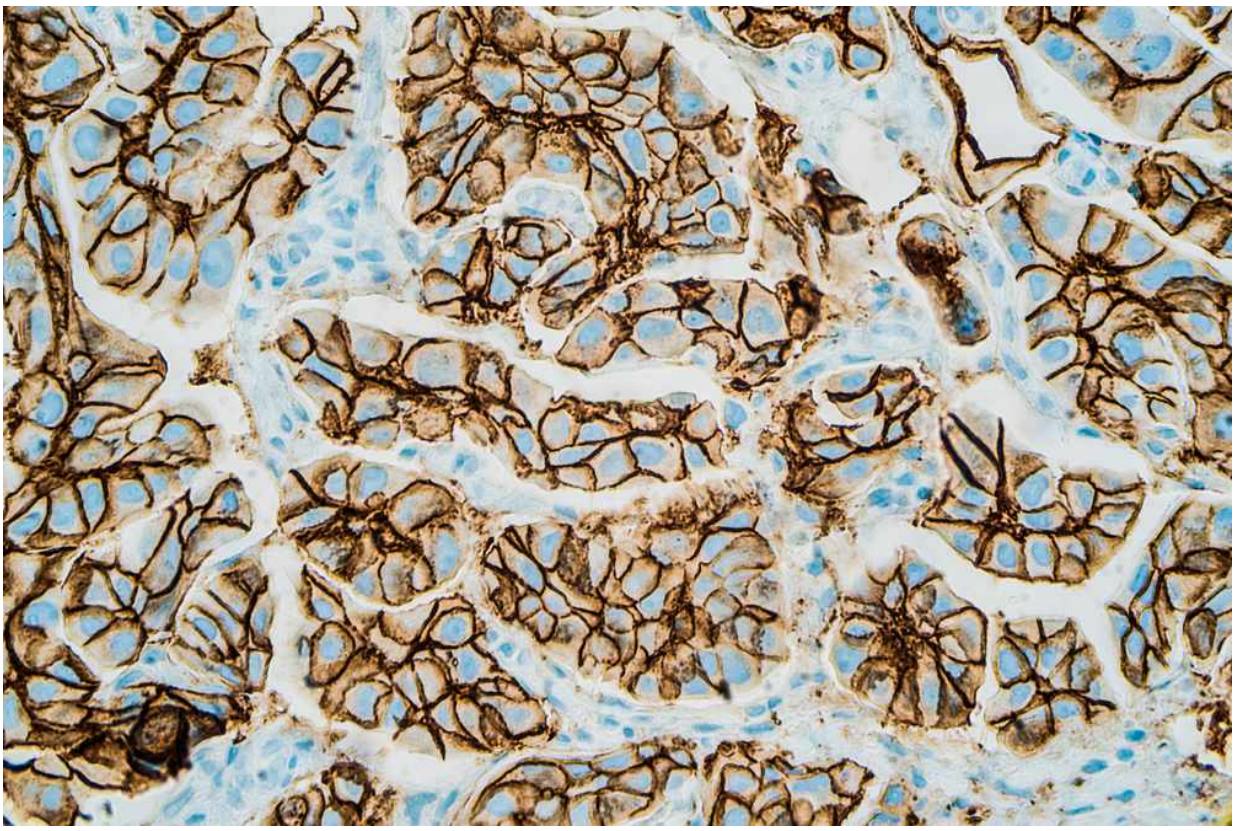

Credit: Mayo Clinic

Changes to HER2 testing guidelines for breast cancer in 2013 significantly increased the number of patients who test HER2-positive,

according to a new study by Mayo Clinic researchers published in the *Journal of Clinical Oncology*. Cancers that have an excess of HER2 protein or extra copies of the HER2 gene are called HER2-positive and can be treated with drugs like Herceptin that target HER2. HER2 stands for human epidermal growth factor receptor 2.

Mayo Clinic researchers found that the number of HER2-positive breast cancers doubled after testing guidelines were changed by the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) in 2013. "The new guidelines were established to reduce the number of equivocal cases, where HER2 status is uncertain, but we found that they did just the opposite," says senior study author Robert Jenkins, M.D., Ph.D., the Ting Tsung and Wei Fong Chao Professor of Individualized Medicine Research and Professor of Laboratory Medicine and Pathology at Mayo Clinic. "The number of equivocal cases went up, resulting in additional testing and a much larger number of women with cancers ultimately labeled as HER2-positive.

According to Breastcancer.org, more than 10 percent of women will develop breast cancer in their lifetime. In the U.S. alone, the American Cancer Society estimates there will be more than 246,000 new cases of invasive breast cancer diagnosed this year, along with 61,000 new cases of noninvasive breast cancer. All newly diagnosed breast cancers are tested for human epidermal growth factor receptor 2 (HER2), a molecule that promotes the growth of cancer cells. HER2-positive cancers tend to be more aggressive and spread more quickly than other breast cancers.

Dr. Jenkins says the development of drugs like trastuzumab (Herceptin) and lapatinib (Tykerb) that target HER2 have greatly improved the prognosis of patients with HER2-positive breast cancer, but it is not clear what level of HER2 is needed on cancer cells for these targeted therapies to be effective. Therefore, he says, it is critical that clinicians

accurately determine the HER2 status of a particular cancer. HER2 testing is performed using two methods: immunohistochemistry, which detects how much of the HER2 protein is present on cancer cells, and fluorescence in-situ hybridization (FISH), which measures how many copies of the HER2 gene are inside each cell.

The U.S. Food and Drug Administration (FDA) approved the first HER2 testing guidelines for determining eligibility for HER2-directed therapy for breast cancer in 1998. The American Society of Clinical Oncology/College of American Pathologists published a new set of guidelines in 2007 (AC2007), which were updated in 2013 (AC2013). The latest guidelines changed the cut-off for equivocal and positive cases.

Dr. Jenkins and his colleagues hypothesized that the new criteria outlined in AC2013 would lead to an increase in the number of breast cancers that test HER2-positive. They analyzed FISH results for 2,851 breast cancer cases referred to the Mayo Clinic Cytogenetics Laboratory for FISH testing between November 2013 and October 2014, and then compared the prevalence of HER2 FISH amplification using the three guidelines.

In their analysis, the researchers found a near doubling in the proportion of HER2 FISH-positive cases interpreted using AC2013 (23.6 percent), compared to the FDA criteria (13.1 percent) or AC2007 (11 percent). The Mayo researchers previously reported a 13 percent HER2-positivity rate using the FDA criteria in their clinical practice in 2000, and that rate had remained constant until the implementation of AC2013. Since the implementation of AC2013, an additional 10-15 percent of women with breast cancer are considered eligible for HER2-directed therapies, even though it is unknown if they would benefit from addition of HER2-directed treatments.

"Women who receive false positive results are not only exposed to the risks of HER2-directed therapies, but they also miss out on the treatments that could be effective against their cancer. That is counter to the goal of personalized medicine, which is to give the right drug to the right patient at the right time," says Dr. Jenkins. "Given the medical, financial and psychosocial aspects of these targeted therapies, it is prudent that we prospectively identify the most optimal candidates for treatment."

Dr. Jenkins says that the recent National Surgical Adjuvant Breast and Bowel Project B-47 trial could provide insight into whether the additional patients labeled as HER2-positive by AC2013 actually will benefit from HER2-directed therapies. Ultimately, he says, the decision to use such targeted therapies should be taken only after carefully considering the risks and benefits by patients and their physicians, as well as any additional information that can be gleaned from other HER2 tests results, including immunohistochemistry.

More information: M. V. Shah et al. Change in Pattern of HER2 Fluorescent in Situ Hybridization (FISH) Results in Breast Cancers Submitted for FISH Testing: Experience of a Reference Laboratory Using US Food and Drug Administration Criteria and American Society of Clinical Oncology and College of American Pathologists Guidelines, *Journal of Clinical Oncology* (2016). DOI: 10.1200/JCO.2015.61.8983

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