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Expert analysis of HER2 tests reveals issues with reliability, researchers say

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Results for testing breast tumors for HER2 proteins and genes is most often straightforward when one piece of tumor (a single tumor block) is analyzed. However, tumors can be diverse, and researchers at Mayo Clinic found that HER2 results can vary in up to 10 percent of patients when several tumor blocks are analyzed.

This could have significant implications for patient treatment, say the researchers, who are presenting their findings at the 33rd Annual CTRC-AACR San Antonio Breast Cancer Symposium.

In their study, the researchers found that while three independent teams of expert pathologists agreed most of the time on how slices from a single tumor block from a patient should be classified in terms of HER2 genes and proteins, a consensus was harder to reach when several blocks from the same patient were available for analysis.

In fact, the pathologists, from central laboratories at Mayo Clinic, the University of Southern California, and the University of Pittsburgh, found significant heterogeneity, or variability, between two tumor blocks taken from the same patient in 5 to 10 percent of cases. Most often, one tumor block showed a normal HER2 expression, while the second piece of tumor tested HER2+.

Researchers say these findings matter because women with HER2+ breast cancer can benefit from Herceptin, a drug designed to shut down a powerful cancer growth pathway.

"Even among expert pathologists there can be disagreements about what a tumor is telling us, and that impacts the care our patients receive," says the study's lead investigator, Edith Perez, M.D., deputy director of Mayo Clinic Cancer Center in Florida.

The findings suggest that patients with multiple tumor samples who test normal for HER2 in one block should consider having the other tumor sample tested, Dr. Perez says. Most oncologists take and store more than one tumor block from their patients, but it is not clear who would fund testing of the second tumor sample, she adds.

This analysis continues the investigation into the reliability of HER2 protein (immunohistochemistry) and gene (fluorescence in situ hybridization, or FISH) tests that Dr. Perez has led since 2001. She and her team published a study in 2002 that found the disagreement between local and central laboratories that analyze these tests was between 15 and 20 percent. Central laboratories process more than 100 patient tumors per year and local labs perform fewer than that amount.

In this study, Dr. Perez wanted to know whether pathologists in the central laboratory agree more often with each other than they do with pathologists at local laboratories.

All three teams of pathologists conducted a blinded review of samples from 389 patients who had been enrolled in three adjuvant clinical trials (N8931, BCIRG005, and BCIRG006) in which HER2 testing was performed by local and central laboratories to determine if patients were candidates for these studies. Each of the three central laboratories received at least six slides from a patient's tumor block that the laboratory used to retest HER2 gene and protein levels.

The goals were to analyze how often the two tests agreed with each other between the laboratories; determine whether an "adjudication" process

could resolve cases that don't agree; ascertain whether two samples from the same tumor agreed with each other; and gauge the impact of anti-HER2 therapy (Herceptin) in patients with disputed results.

Researchers found that there was 92 percent agreement between the two tests.

Then, the pathologists met face to face to discuss the 8 percent of tumor samples that they did not initially agree on, and reached consensus on 96 percent of the HER2 protein tests and 97 percent of the gene tests. The disagreement most often occurred in HER2 tests that were borderline for the established threshold of HER2+ positivity, Dr. Perez says.

They then looked at 125 patients (in the group of 389) who had more than one tumor block available for analysis. They found that 5 to 10 percent of these samples had dissimilar protein and gene test results.

This variability was greater than suspected, she says. "Some people have reported heterogeneity to be only 1 percent."

The slices from a tumor that make up a tumor block are made very close to each other (a distance of 6 microns) and a second tumor block can be made in the same tumor but at a distance from the original tumor slice. Biological variability can exist within a tumor for a number of reasons, Dr. Perez says. "The stroma surrounding a tumor can have a different impact on growth proteins that are expressed in one part of a tumor, compared to another, and development of pathways that lead to HER2-positivity may not occur at the same time in a tumor."

Finally, the researchers looked at how patients with these dissimilar tumor blocks were treated. In most cases, these patients had been diagnosed as HER2 normal, but the second tumor block tested as HER2+. "These patients may not have been diagnosed correctly and that

is a big issue," says Dr. Perez. "It suggests that when a second tumor block is available in patients who test normal, it could be tested to validate these results."

This finding helps explain why some breast cancer patients who had normal HER2 results but who were still treated with Herceptin responded well to the treatment, she adds. "This may dispel the notion that Herceptin may be of benefit in women with truly normal HER2 tumors."

And the disagreement seen throughout this study can also help explain some of the variability in results seen between central and local laboratories, Dr. Perez says.

"It is necessary for oncologists to continue to refine these tests and their analysis," she says. "That may mean some tests may be needed for multiple tumor blocks, or that pathologists may need to discuss borderline results for some patients."

Provided by Mayo Clinic