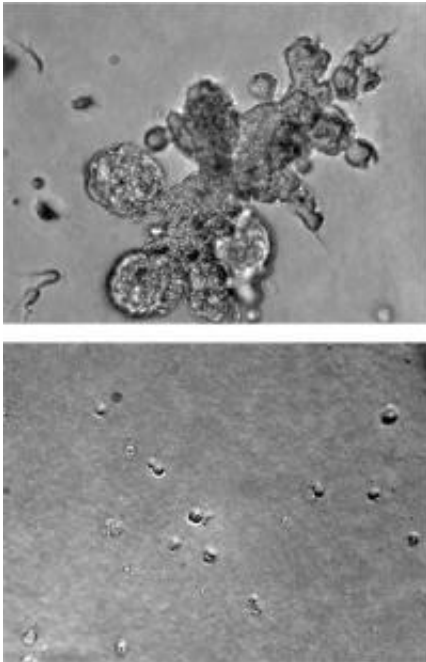


Existing drugs may help more breast cancer patients

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The top image shows untreated breast cancer cells with HER2 mutations. The bottom image shows how much these cells shrink after treatment with neratinib, an anti-HER2 drug currently in clinical trials. Credit: Ron Bose

More patients can benefit from highly effective breast cancer drugs that are already available, according to DNA sequencing studies by researchers at Washington University School of Medicine in St. Louis and other institutions.

The investigators found that some women with the HER2 negative subtype may benefit from anti-HER2 drugs even though standard tests don't indicate they are candidates for the drugs.

"These patients are going to be missed by our routine testing for HER2 positive [breast cancer](#)," says Ron Bose, MD, PhD, assistant professor of medicine. "Currently they're not going to receive a HER2 targeted drug because we don't have a way to identify them. And we predict they are going to have a more aggressive form of breast cancer."

Bose, who treats patients at Washington University's Siteman Cancer Center at Barnes-Jewish Hospital, will present the data Dec. 7 at the San Antonio Breast Cancer Symposium.

Today, a type of breast cancer known as HER2 positive is treated with drugs that inhibit the function of the [HER2 protein](#). To be classified as HER2 positive, a patient must have more than the normal two copies of the [HER2 gene](#). Too much HER2 drives [tumor growth](#) and some HER2 positive patients may have as many as 20 copies of the gene. Doctors test for this gene "amplification" in every patient diagnosed with breast cancer. It must be present for a woman to receive anti-HER2 drugs.

But instead of multiple copies of the gene churning out too much HER2, some patients deemed HER2 negative based on standard testing may have mistakes in just a few "letters" of the DNA in their two gene copies that result in excess activity of the protein. Bose and his colleagues estimate that these undetected HER2 [mutations](#) – rather than the HER2 amplification—may be driving tumor growth in 1.5 to 2 percent of all [breast cancer patients](#). With about 230,000 new cases of breast cancer diagnosed in the United States each year, even this modest percentage translates into more than 4,000 patients per year.

The study, led by senior author Matthew J. Ellis, MD, PhD, of

Washington University, and published online Dec. 7 in the journal *Cancer Discovery*, analyzed data from eight DNA sequencing studies, which together included about 1,500 patients. Two of the sequencing studies were conducted by The Genome Institute at Washington University, in collaboration with study co-author Elaine R. Mardis, PhD, co-director of the genome institute.

Of the 1,500 patients, 25 were found to have HER2 mutations without [gene amplification](#). Not all mutations appeared to have the same effect, however. After analyzing 13 of the mutations, seven were found to drive cancer growth. In the laboratory analysis, most of these mutations responded well to the anti-HER2 drugs lapatinib and trastuzumab, both approved by the U.S. Food and Drug Administration. Although two of the mutations were resistant to lapatinib in lab tests, they responded well to neratinib, a newer anti-HER2 drug that is currently in phase II clinical trials.

Bose also cautions that some mutations were found to be "silent," meaning they did not drive the tumor's growth and therefore would likely not respond to anti-HER2 drugs.

The study's findings have led directly to the launching of a phase II clinical trial to test whether patients with HER2 mutations (but not the amplification) will benefit from anti-HER2 drugs. The trial will include patients with stage IV breast cancer classified as HER2 negative. Their HER2 genes will be sequenced to look for mutations. If mutations are present, they will be treated with neratinib in addition to the standard treatment they would otherwise receive.

At Washington University, the trial will be led by Cynthia X. Ma, MD, PhD, associate professor of medicine. The other centers participating in the study are the Dana-Farber Cancer Institute, Memorial Sloan-Kettering Cancer Center and the University of North Carolina, Chapel

Hill.

Bose points to this study as an example of the potential value in sequencing the DNA of cancer patients, even when limited to a single gene of interest such as HER2.

"If we can identify mutations that we can act on, that information will help us better guide treatment," Bose says. "In this case, we don't even have to develop new drugs against HER2 mutations. It's just a matter of finding the patients."

Provided by Washington University School of Medicine

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