

Coming closer to delivering on the promise of personalized breast cancer therapy

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A team led by researchers at Baylor College of Medicine is coming closer to delivering on the promise of personalized breast cancer therapy with a strategy to predict the most likely response of a cancer to a specific less toxic treatment regimen.

In this study published in *Clinical Cancer Research*, the scientists developed and validated in [clinical trials](#) a multiparameter molecular classifier test to predict with a high degree of confidence which patients with HER2-positive (HER2+) [breast cancer](#) would be candidates for anti-HER2 therapy alone without the need for chemotherapy. The molecular classifier also accurately identifies patients whose tumors may need chemo or other targeted therapies.

"HER2+ breast cancer, which represents about one of every five breast cancers, expresses high levels of HER2 proteins and is physiologically dependent on the abundance of this protein to grow fast and metastasize or spread to other organs," said co-corresponding author Dr. Rachel Schiff, professor of medicine and molecular and [cellular biology](#) and member of the Lester and Sue Smith Breast Center and the Dan L Duncan Comprehensive Cancer Center at Baylor. "Historically, HER2+ breast cancer was treated only by chemotherapy, but patient outcomes were poor. This changed in the late 1990s when the introduction of anti-HER2 therapy, drugs that block the growth effects of HER2, transformed the treatment of this disease."

The Schiff-Osborne lab and colleagues, along with author Dr. Mothaffar F. Rimawi, professor of medicine, executive medical director and co-leader of the Breast Cancer Program of the Dan L Duncan Comprehensive Cancer Center, have been studying for years the most effective approach to treat HER2+ breast cancer.

They had previously determined that specifically targeting the HER2 protein with two anti-HER2 drugs (lapatinib and trastuzumab) before

surgery resulted in a complete response—meaning disappearance of all cancer in the breast—in about 25-30% of cases to the extent that chemotherapy, which typically is part of the treatment, was no longer needed, sparing patients the toxic effects and cost of chemo. The challenge was to identify those 30% at the time of diagnosis.

"These findings suggested that a subset of HER2+ breast cancers is so addicted to HER2 and that identifying such patients would permit a therapy de-escalation approach," said Rimawi. "We then worked to develop a strategy that would allow us to distinguish the patients who would respond to anti-HER2 treatment without chemo from those who would need chemo."

"We successfully developed and independently validated a multiparameter molecular test on samples from the tumor that helps us predict at the time of diagnosis the most likely response of a tumor to anti-HER2 therapy alone without chemotherapy, therefore identifying patients who may benefit from chemo-sparing dual HER2-targeted therapy alone," said first author Dr. Jamunarani Veeraraghavan, assistant professor of the Lester and Sue Smith Breast Center and member of Dan L Duncan Comprehensive Cancer Center at Baylor.

The molecular classifier has three components. "The first component measures how much HER2 gene and protein is in the cancer cells and whether the expression is homogeneous throughout the tumor," Veeraraghavan said. "All [tumor cells](#) must express high levels of HER2 for a higher chance of a complete response."

The second component analyzes whether the cancer expresses a set of genes reflecting the cancer's growth dependence on HER2 (called HER2-enriched). Finally, the third component looks into the gene PIK3CA. Mutations in this gene bypass HER2-driven pathways providing alternative molecular roads for the cancer cells to grow when

the HER2 protein is blocked.

"We tested our molecular classifier on tumor samples from two of our previous clinical trials," Veeraraghavan said. "To be a candidate for HER2 therapy without chemo, a tumor must fulfill all of the above-mentioned characteristics."

"In addition to identifying patients who may benefit from dual HER2-targeted therapy alone, the classifier also can accurately identify patients whose tumors are not HER2-addicted and therefore may not be good candidates for treatment de-escalation (without chemo), which is crucial for a safe de-escalation approach," Schiff said.

"Traditionally, in an effort to eliminate the tumor we give patients more aggressive treatments, but these also increase the toxicity and affect the patient's quality of life," said Veeraraghavan. "But when we provide a personalized treatment, we are giving patients what they need to treat the tumor, not more, minimizing the consequences on their quality of life. This is an important aspect of precision medicine that we do not want to miss."

"Studying the biology of the tumor tells us what would be needed to eliminate the [tumor](#). Our findings strongly support that safe treatment de-escalation is possible," Rimawi said. "We are next evaluating the molecular classifier in a prospective clinical trial to further validate its clinical utility. If validated prospectively, our classifier may function as a molecular triaging tool to safely and appropriately select patients with HER2+ breast cancer for treatment de-escalation."

"This discovery is the product of many years of research," said co-author Dr. C. Kent Osborne, Dudley and Tina Sharp Chair for Cancer Research, professor of medicine-hematology-oncology and founding director of the Dan L Duncan Comprehensive Cancer Center at Baylor.

"We first observed that blocking HER2 with two different drugs in breast [cancer cells](#) growing in culture was superior to one drug, and then we confirmed this in mice with HER2+ human tumors. The tumors disappeared quickly in all mice, something we had never seen before. We then translated these discoveries to patients and found the same rapid disappearance of all cancer in about a third of them. Now we think we have a way of identifying these patients so we can give them the proper treatment for their cancer rather than giving the same treatment to all patients."

More information: Jamunarani Veeraraghavan et al, A multiparameter molecular classifier to predict response to neoadjuvant lapatinib plus trastuzumab without chemotherapy in HER2+ breast cancer, *Clinical Cancer Research* (2023). [DOI: 10.1158/1078-0432.CCR-22-3753](#)

Provided by Baylor College of Medicine

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