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Roots of resistance to cancer drugs runs deeper than a single gene

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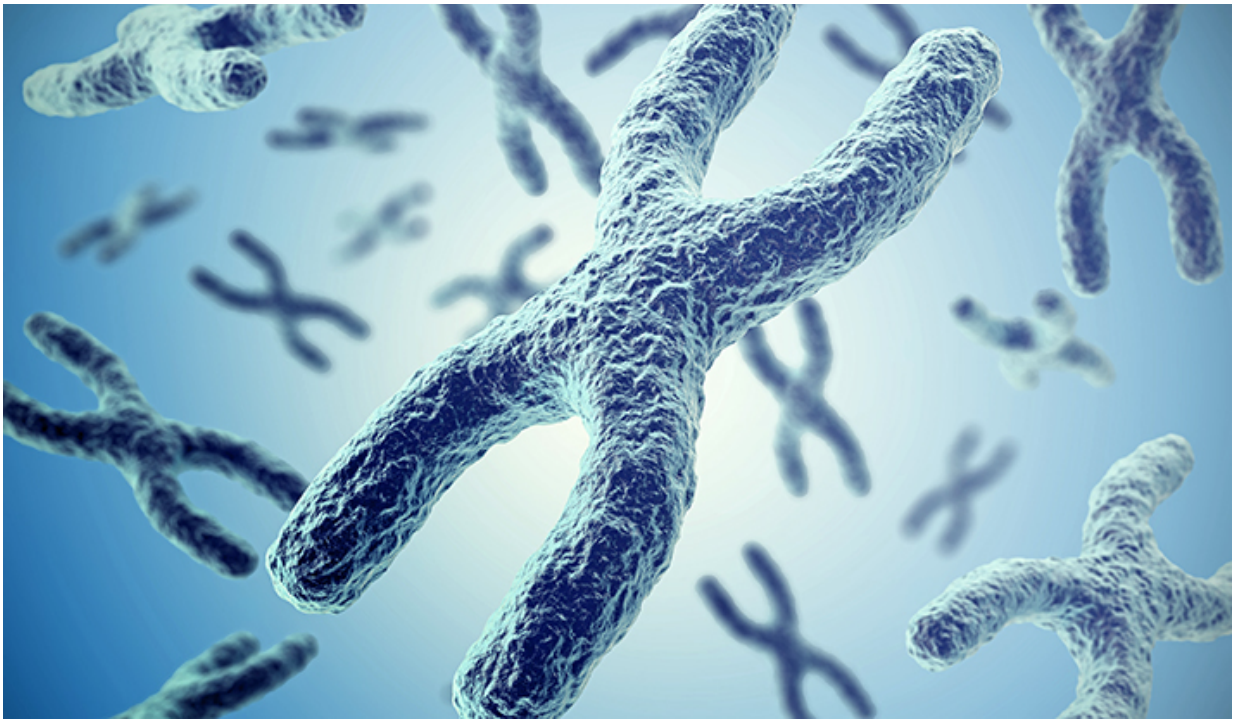

Credit: stock.adobe.com

Searching for more individual genes to predict responses to breast cancer therapy may not work, a new study suggests. Instead, scientists and clinicians need to pay attention to abnormalities in networks of genes, Yale researchers report in a paper published Oct. 10 in the journal *Annals of Oncology*.

The Yale team studied all the genes of 200 patients who had HER2-positive breast cancer (about 15% of breast cancers have too many copies of the HER2 gene). About half of the patients responded very well to HER2-targeted therapy, but half did not, researchers reported. However, they were not able to find a single gene abnormality that could serve as a biomarker to predict treatment outcomes for all patients.

"If we keep looking for one marker at a time, we will not find a clinically useful marker to guide treatment selection for these drugs," said Dr. Lajos Pusztai, researcher at the Yale Cancer Center and senior author of the study.

However, they did find abnormalities in several dozens of genes in a single molecular network that aid in transmitting chemical information from the HER2 molecule on the cell surface to the interior of the cell. The presence of these abnormalities predicted which patients would be resistant to standard therapies. Only few patients, however, shared the same individual abnormalities, and the network was affected at different genetic locations in different patients.

"You can look at these treatment-resistant cancers like a broken car—there are many different ways for a car to break down but the outcome is the same: The car is not working," Pusztai said.

He said a diagnostic test that can pinpoint abnormalities in this network of genes might help customize treatment. A new generation of drugs to treat women with HER2-positive breast cancer are now available and are effective, but are also extremely costly, Pusztai said. "We could save this new generation of drugs for those who really need it and treat women who don't with therapies that are less intense."

More information: W. Shi et al. Pathway level alterations rather than

mutations in single genes predict response to HER2-targeted therapies in the neo-ALTTO trial, *Annals of Oncology* (2016). DOI: 10.1093/annonc/mdw434