

A Multimodal AI Model May Improve Recurrence Risk Stratification in Early Breast Cancer

New model provided better prognostic information for recurrence of HR-positive/HER2-negative breast cancer.

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SAN ANTONIO – An artificial intelligence (AI) model created by integrating clinical, molecular, and histopathological data significantly improved recurrence risk stratification in hormone receptor (HR)-positive, HER2-negative [breast cancer](#), according to results presented at the [San Antonio Breast Cancer Symposium](#) (SABCS), held December 9-12, 2025.

HR-positive, HER2-negative breast cancer is the most common subtype of breast cancer, and at least 50% of all recurrences in this subtype occur more than five years after diagnosis, explained [Joseph A. Sparano, MD](#), chief of the Division of Hematology and Oncology at the Mount Sinai Tisch Cancer Center. The Oncotype DX (ODX) 21-gene recurrence score, a unimodal molecular test that provides prognostic information for distant recurrence and predictive information for chemotherapy benefit, is widely used in clinical practice, although its ability to forecast recurrence after the five-year mark is limited, Sparano noted.

“Our goal was to develop a new diagnostic test that provides better prognostic estimation of recurrence risk, including late recurrence risk, by studying tumor specimens from the TAILORx trial,” said Sparano. “We developed an AI model that evaluates both the images of digitized slides used for routine pathologic assessment, plus the molecular and clinical characteristics of a breast cancer to provide better prognostic information about cancer recurrence risk out to 15 years, including early recurrence within five years after diagnosis, and late recurrence after five years,” he continued. This involved the development of a new molecular test that included an expanded panel of genes derived from five commercially available gene assays, including the ODX.

The research team used digitized tissue images and molecular RNA expression data from 4,462 tumor samples and corresponding clinical data from TAILORx study participants. These data were used to train and validate several risk models. The prognostic performances of the models were compared to the performance of ODX results used in the trial to guide chemotherapy use, and were assessed using the concordance index (C-index). The C-index is a statistical test that measures the ability of a diagnostic test to correctly rank recurrence risk. A C-index of 0.5

indicates a test that performs no better than chance, whereas a C-index of 1 indicates perfect prognostication.

ICM+, a multimodal model integrating the pathomic imaging (I), clinical (C), and expanded molecular (M+) models, performed significantly better than the ODX for overall distant recurrence at 15 years (C-index 0.705 vs. 0.617) and late recurrence after 5 years (C-index 0.656 vs. 0.518) in the training/5-fold cross validation set including 2,806 patients. ICM+ also exhibited similar superior prognostic performance compared with ODX in a holdout validation set including 1,621 patients for overall recurrence (C-index 0.733 vs. 0.631) and late distant recurrence (C-index 0.705 vs. 0.527).

The findings from this study will ultimately result in the availability of a new diagnostic test that more reliably estimates recurrence risk in women with HR-positive, HER2-negative, node-negative breast cancer, which accounts for about one-half of all breast cancers in the United States, explained Sparano.

“This study shows the potential for how AI can be leveraged to develop better diagnostic tests that may more accurately estimate recurrence risk and individualize treatment decisions,” said Sparano. Currently available molecular assays, whether performed in a central reference lab or CLIA-certified local laboratory, require sophisticated instrumentation and technical expertise, he noted. “AI-based pathomic tools that rely on evaluation of tissue sample slides routinely generated from clinical practice can be captured with scanners or even widely available smartphones, uploaded electronically, and analyzed centrally with minimal cost,” he added.

A limitation of the study is that it was not designed to develop tests that are predictive of chemotherapy benefit or benefit from continuing adjuvant endocrine therapy beyond five years, said Sparano.

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Sparano serves as a consultant for AstraZeneca, Delphi Diagnostics, Genentech, Genomic Health/Exact Sciences, Novartis, and Pfizer; is a member of the scientific advisory board for PreciseDX; and receives institutional research support from Olema Oncology.

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