

Artificial Intelligence Can Help Identify HER2-Low and HER2-Ultralow Breast Cancer

Accurate classification of breast cancer receptor status can help guide treatment decisions, making more patients eligible for HER2 targeted therapies.

May 28, 2025 By Liz Highleyman, adapted from ASCO

Using artificial intelligence (AI) assistance can help pathologists more accurately classify breast cancer with low levels of HER2 expression and reduce the risk of misclassifying HER2-low and HER2-ultralow tumors as HER2-negative, according to study results to be presented at the [2025 American Society of Clinical Oncology \(ASCO\) Annual Meeting](#) taking place May 30 to June 3 in Chicago. This can make more patients with HER2-low or HER2-ultralow breast cancer eligible for HER2 targeted therapies, such as Enhertu (fam-trastuzumab deruxtecan).

Breast cancer is classified by the type of receptors on tumors. Most have estrogen or progesterone receptors that make them treatable with hormone therapy, classified as HR-positive. Around 15% to 20% of breast tumors have high expression of HER2, classified as HER2-positive. However, a majority of tumors traditionally classified as HER2-negative actually have some HER2 receptors, now classified as HER2-low, and perhaps 25% are HER2-ultralow. Triple-negative breast cancer doesn't express any of these receptors and is harder to treat.

“Roughly 65% of breast tumors once called HER2-negative actually demonstrate some level of HER2 expression and belong to subgroups now classified as HER2-low or HER2-ultralow breast cancers,” said lead study author Marina De Brot, MD, PhD, of A.C. Camargo Cancer Center in Brazil, in an [ASCO news release](#). “Some of these tumors could be treated with HER2-targeted drugs but only if we detect their HER2 expression levels. Our study provides the first multinational evidence that artificial intelligence can help close a critical diagnostic gap and open the door to new therapies, like antibody-drug conjugates, for a majority of patients who until recently had not been offered these options.”

In 2019, the Food and Drug Administration [initially approved](#) the antibody-drug conjugate Enhertu for inoperable or metastatic breast cancer with high HER2 expression. Approval was extended [to patients with HER2-low breast cancer](#) in 2022 and [to those with HER2-ultralow tumors](#) this past January.

But it can be challenging and time-consuming for pathologists to accurately identify HER2 protein expression in HER2-low and ultralow breast cancer using traditional immunohistochemistry (IHC) testing that looks for HER2 proteins in tumor tissue samples. In situ hybridization (ISH) is a technique that uses labeled probes to identify specific nucleic acid sequences within cells or tissues. HER2-low breast cancers have a HER2 IHC score of +1 or +2/ISH negative. HER2-ultralow breast cancers have an IHC score of 0 with membrane staining.

An accurate diagnosis relies primarily on the accuracy of the human eye for detecting abnormalities. Even among experienced breast pathologists, about one in three HER2-ultralow breast tumors can be mistakenly classified as HER2-negative, which usually means that oncologists do not recommend HER2-targeted antibody drug conjugates.

[In this study](#), researchers used an AI-supported digital training platform called ComPath Academy to assist pathologists with their HER2 scoring of breast cancer samples. The study included 105 pathologists from 10 countries in Asia and South America who were tasked with performing a HER2 assessment of 20 digital breast cancer cases, both with and without AI assistance.

Over the course of five sessions, the pathologists performed a total of 1,940 readings that were done during three separate exams. AI support was only offered during the third exam. Their readings were then compared against ground-truth IHC scores from a central reference center. Ground-truth scores are arrived at by a consensus among multiple expert pathologists who independently review and score HER2 IHC-stained tissue samples and have been established as the gold standard reference for determining HER2 breast cancer status.

The study found that with AI assistance:

- Scoring sensitivity rose from approximately 76% to 90%, and pathologists' agreement with the central reference scores improved by about 13%. Using AI support, the pathologists had an average agreement of 89.6% with the central reference scores versus 76.3% without AI assistance.
- The pathologists' accuracy in correctly identifying cases as HER2-positive, HER2-low, HER2-ultralow or HER2-negative also improved by nearly 22%. Their accuracy in categorizing the cases increased from 66.7% without AI support to 88.5% with AI assistance.
- AI assistance reduced how many HER2-ultralow cases were misclassified as HER2-negative by more than 25%. Only 4% of readings were misclassified when pathologists used AI assistance compared to the 29.5% of readings that were misclassified when AI assistance was not used.

The researchers are now planning multicenter implementation studies that embed the AI tool in routine diagnostics to measure clinical effects, including changes in treatment options and time to

treatment for patients with HER2-low and HER2-ultralow breast cancer.

“Accurate HER2 scoring is important to ensure that patients receive the best treatment for their breast cancer. This international study shows that an AI-assisted approach improved HER2 scoring, including in situations that would affect treatment decisions,” said ASCO AI expert Julian Hong, MD, MS, of University of California San Francisco. “These findings shed light on the promising role for AI in oncology, not as a replacement for the physician but as a powerful tool to help us work smarter and faster to deliver high-quality, more personalized care.”

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This report is adapted from a [news release](#) published by the American Society of Clinical Oncology on May 22, 2025.

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