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The American Society of Clinical Oncology–College of American Pathologists Guideline Update for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer

How Low Can HER2 Go?

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In an accompanying article, Wolff et al[1] provide an update to the American Society of Clinical Oncology (ASCO)-College of American Pathologists (CAP) guideline for human epidermal growth factor receptor 2 (HER2) testing that specifically addresses the identification of "HER2-low" breast cancers, that is, those tumors that exhibit an immunohistochemistry (IHC) score of 1+ or 2+ without gene amplification using the 2018 ASCO-CAP HER2 guideline criteria.[1,2]

See also Wolff AC, Somerfield MR, Dowsett M, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO–College of American Pathologists Guideline Update.

Why is this important for pathologists? The results of the DESTINY-Breast04 (DB-04) phase 3 trial, published in June 2022, demonstrated the efficacy of the anti-HER2 antibody-drug conjugate (ADC) trastuzumab-deruxtecan (T-DXd) in patients with HER2-low metastatic breast cancer, with a significant and meaningful improvement in progression-free and overall survival over conventional chemotherapy.[3] This, in turn, led to rapid approval by regulatory agencies and implementation in international treatment guidelines. It also led to pathologists suddenly being tasked with how best to identify HER2-low breast cancers as accurately and reproducibly as possible, something that they had not been required to do since routine testing of breast cancers for HER2 began almost 24 years ago.

Unfortunately, this new task is not at all straightforward for several reasons. First, the IHC assays the pathology community has been using to detect HER2-positive breast cancers since the Food and Drug Administration approval of trastuzumab in 1998 were intended to identify tumors with high levels of HER2 protein overexpression. These assays do not have the sensitivity or dynamic range to reliably identify tumors with low levels of protein on the tumor cell surface and were not developed to be used for that purpose. In fact, although the 3 prior versions of the ASCO-CAP HER2 guideline (published in 2007, 2013, and 2018) provided criteria for distinguishing HER2 0 from HER2 1+ cases,[2,4,5] this distinction was clinically irrelevant until the publication of the DB-04 results. Therefore, for more than 2 decades, many pathologists have simply reported cases that showed 1+ or 0 HER2 staining as "HER2-negative (0 or 1+)." Second, details regarding preanalytic and analytic factors are likely to have a major impact on accurately identifying HER2-low cases, including cold ischemic time, fixation time, decalcification procedures for bone biopsies, epitope retrieval protocols, choice of primary antibody, detection system, and signal enhancement protocols. For example, prior studies have demonstrated that the antibody used in HercepTest is more sensitive for identifying HER2 1+ cases than the antibody used to determine eligibility for DB-04 (clone 4B5).[6] Third, studies have shown that the distinction between HER2 0 and 1+ cases is subject to considerable interobserver variability.[7,8] In short, pathologists have now been put in the position of having to use an IHC assay for a purpose for which it was not developed, to make nuanced distinctions in the interpretation of HER2 stains that have poor reproducibility. Finally, several studies have demonstrated that the HER2-low phenotype may change over time within a given patient, with cases converting from HER2 0 to HER2 1+ and vice versa between the primary tumor and subsequent recurrences in about 40% of patients.[9,10] This raises the challenge of which sample (and even how many

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blocks per sample) to test for any given patient to determine if the tumor is HER2-low.

The issue of identifying HER2-low breast cancers is further complicated by the uncertainty about whether or not patients with tumors categorized as HER2 0 will respond to ADCs such as T-DXd, since these patients were not included in the DB-04 trial. Limited data from the single-arm phase II "DAISY" study suggest that T-DXd may harbor relevant antitumor activity even in patients with HER2 0 tumors, with an objective response rate of 30%.[11] While the ongoing DESTINY-Breast-06 phase 3 trial includes a subset of patients with HER2 0 tumors (those with HER2 IHC >0 and <1+, considered by some as HER2 "ultralow"), this trial does not include patients with tumors with no HER2 protein expression at all (considered by some as HER2 "null").[12] Nevertheless, if clinical trials ultimately demonstrate that patients with HER2 0 tumors have a response rate to ADCs similar to that seen in HER2-low tumors, the attempt to distinguish HER2 1+ from HER2 0 cases may become clinically irrelevant, and the current efforts to make this distinction will have been a tempest in a teapot.

But at least for now, pathologists are required to distinguish between HER2 1+ and HER2 0 cases on a routine basis with the tools currently available. To that end, the ASCO-CAP guideline update offers several pragmatic best practices to aid pathologists in making this distinction.[1] These include the following: continuing to score HER2 IHC using the 2018 ASCO-CAP guidelines; examining HER2 IHC at high-power magnification when attempting to distinguish 1+ from 0 staining; considering review by a second pathologist for cases on the borderline between 0 and 1+; using controls with a range of protein expression, including 1+ cases; and paying careful attention to preanalytic factors. In addition, the guideline recommends including a comment in HER2 reports stating that patients with HER2 1+ or 2+ staining without gene amplification may be eligible for a treatment that targets nonamplified or non-overexpressed levels of HER2 expression for cytotoxic drug delivery.[1]

What does this guideline update *not* do? It does not recommend using "HER2-low" terminology in our reports since "there is no evidence that 'HER2-low' is a new or reproducibly defined subtype of breast cancer with distinct prognostic or predictive implications."[1,10] Further, it is not possible to apply HER2-low terminology consistently when reporting HER2 IHC results. Specifically, while HER2 1+ cases could be categorized as HER2-low based on IHC alone, it is not possible to know if any given HER2 2+ case is HER2-low or HER2-positive until the results of an in situ hybridization assay for HER2 gene amplification are available. The guideline update also does not recommend changes to the traditional terminology of "positive," "equivocal," and "negative" for HER2 IHC results. However, it should be remembered that these terms were initially created specifically to identify patients likely (or unlikely) to benefit from trastuzumab therapy. Now that the use of HER2 IHC testing has been expanded to also identify patients with HER2-low tumors, these qualitative terms do not always have their original meaning and have the potential to create confusion. For example, while HER2-low tumors are negative with regard to benefit from conventional HER2-targeted antibody therapy, they are not negative with regard to their potential response to ADCs. It remains to be seen whether shifting to reporting only the numeric score for HER2 IHC results, unqualified, provides better clarity in conveying the information needed for treatment decisions in current clinical practice. While the guideline update also does not endorse the use of newer methods to quantify HER2 protein levels at the present time, newer technology such as quantitative immunofluorescence assays[13] and the use of artificial intelligence algorithms applied to digitized slides[14] may be particularly well suited for HER2 quantification in a consistent and reproducible manner if a clinical need persists.

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