COLLEGE of AMERICAN PATHOLOGISTS

Topic: **HER2 Testing in Breast Cancer: Guideline Update**
Date: June 7, 2023

What was the impetus of this guideline update?
In 2022, based on results of the DESTINY-Breast04 trial, the United Stated Food and Drug Administration (FDA) expanded the approval of the HER2 antibody-drug conjugate, trastuzumab deruxtecan, from metastatic breast cancer patients with HER2 protein over-expression/amplification to also include metastatic patients with HER2 IHC 1+ or 2+/ISH negative results. This clinical trial adopted new terminology, "HER2 Low," as short-hand for the HER2 IHC 1+ or 2+/ISH negative breast cancer cases that were in the trial (patients with IHC 0 results were excluded). Since the CAP/ASCO Guideline does not include "HER2 Low" as an interpretive category, a systematic review of the literature was performed to determine if changes to the guideline were needed.

The guideline recommendations did not change from the previous iteration. Why not?
Because DESTINY-Breast04 did not include patients with HER2 IHC 0 results, there is not currently evidence to support that IHC 1+ or 2+/ISH negative results are predictive of trastuzmab deruxtecan treatment response when compared to IHC 0 results (ie no new predictive threshold was validated). Therefore, the FDA expansion of approval to this group was only based on clinical trial eligibility criteria rather than a new predictive indication for HER2 testing. Because DESTINY-Breast04 used the 2018 Guidelines HER2 IHC semi-quantitative scoring system for determining eligibility, the same scoring system is still recommended.

Why doesn't the guideline support the use of a "HER2-Low" interpretative category?
The guideline panel did not find evidence that "HER2 Low" was a prognostic or predictively distinct result category. The panel had concerns that changing the interpretation of HER2 IHC 1+ and 2+/ISH negative to "HER2 Low" would incorrectly imply that breast cancer samples with HER2 IHC 0 results ("HER2 Negative") do not contain low levels of HER2 protein expression. HER2 IHC assays were designed to distinguish high levels of protein over-expression due to gene amplification from those that lack over-expression and not to accurately detect and distinguish protein levels in the lower range of expression. Available data support that HER2 IHC 0 vs 1+ results are not consistent across samples (primary versus metastatic) and that more sensitive assays do in fact identify the frequent presence of low levels of the HER2 protein in IHC 0 samples. More data from clinical trials that include IHC 0 results are needed to determine if these cancers also contain enough HER2 protein for trastuzumab deruxtecan response or if there is a definable "HER2 Low" category using another assay that can predict response. The limited clinical trial data currently available from the single arm DAISY trial suggest that metastatic patients with IHC 0 results may respond similar to those with IHC 1+ results.

How can laboratories help ensure eligibility for trastuzumab deruxtecan without a "HER2-Low" category?
Including the HER2 IHC semi-quanititative results (0,1+,2+ and 3+) in all reports along with the interpretation (negative, equivocal or positive for protein over-expression) is sufficient to identify which patients are eligible for trastuzumab deruxtecan (once reflex ISH testing is performed for IHC 2+ cases). Metastatic breast cancer patients with HER2 IHC 1+ or 2+/ISH negative results (on either the primary or metastatic sample) can be considered for treatment if they meet other clinical eligibility criteria. There are no CAP or federal requirements to use the term "HER2-Low" in breast cancer reporting.

The guideline recommends including a new HER2 testing report comment (see "The Bottom Line" section in the guideline manuscript) that expands on the updated clinical significance of specific HER2 test results.

Best practices for distinguishing IHC 0 vs 1+ include using ASCO/CAP recommended scoring critieria, reviewing at 40x to detect faint or focal areas of expression, considering second reviews for cases close to the threshold and using controls with a range of protein expression.

Our laboratory has decided to use "HER2-Low" as an interpretive category anyway, what should we be aware of?
Be aware that "HER2 Low" terminology is not currently endorsed by ASCO/CAP or NCCN guidelines. The ongoing DESTINY-Breast06 trial and other future trials may further expand the indication for trastuzumab deruxtecan to include some patients with IHC 0 results by current scoring criteria.

Notwithstanding, the CAP Cancer Protocols includes a note addressing "HER2-Low" in the breast resection and biomarker templates. The comment is not an endorsement of or a recommendation to report "HER2-Low." Laboratories may find it helpful, however. The CAP Cancer Committee and the authors of relevant protocols consider the note to be in alignment with CAP/ASCO guideline update.

Did the testing algorithm from the previous guideline update change?
No. The testing algorithm remains unchanged.

Have any of the requirements of the CAP Laboratory Accreditation Program (LAP) changed due to the guideline update?
No. The same requirements apply. Current checklist requirements regarding HER2 assay validation, specimen fixation, proficiency testing, and use of the ASCO/CAP scoring criteria for reporting results are included in the Anatomic Pathology (ANP), Cytogenetics (CYG), and Molecular Pathology (MOL) checklists.

Have CAP Proficiency Testing (PT) requirements changed?
Yes. LAP revised PT and alternative performance assessment (APA) requirements for the 2023 program year. Review COM.01520 for full details. The changes are as follows:

- Laboratories that perform both HER2 IHC stain and interpretation for primary breast carcinoma at the same laboratory must participate in a CAP-accepted PT program.
- Laboratories that perform HER2 IHC interpretation only or HER2 IHC stain only for primary breast carcinoma must perform APA at least semiannually.

Can a laboratory enroll and participate in PT if the lab only performs the interpretation to meet the alternative assessment requirement (slides are stained at a different laboratory)?
Yes. For activities requiring alternative performance assessment, laboratories may use PT products. If the laboratory chooses to enroll in PT they may send the PT slides to an outside laboratory for staining only, and they must only receive back the stained PT slide or an image of the stained PT slide. The laboratory cannot receive quantitative image analysis data from the outside staining laboratory as that would constitute PT Referral by CMS and can have serious consequences.

Note: For laboratories that are concerned about PT referral, the laboratory may use PT samples AFTER the PT event due date and self-evaluate results with the Participant Summary. The laboratory will receive automated email notices from the PT provider reminding them to submit PT results, but these can be disregarded.

Can a laboratory enroll and participate in PT if the lab only performs IHC staining to meet the alternative assessment requirement (slides are interpreted at a different laboratory)?
Yes. For activities requiring alternative performance assessment, laboratories can use PT products. The staining laboratory must have a pathologist onsite that can interpret and report the PT results. The staining laboratory cannot send the slides to another laboratory for assessment/interpretation. This would constitute PT referral by CMS and can have serious consequences.

Note: For laboratories concerned about PT referral, the laboratory may use PT samples AFTER the PT event due date and self-evaluate results with the Participant Summary. The laboratory will receive automated email notices from the PT provider reminding them to submit PT results, but these can be disregarded.

Where are the most current resources and information for this guideline?
A list of the most up-to-date tools and resources can be found on the HER2 Testing in Breast Cancer guideline webpage on cap.org.

What should laboratories expect next?
The CAP will be monitoring the literature, awaiting results of the next DESTINY clinical trial, which includes some IHC 0 cases, as well as other relevant studies outside the clinical trial to determine if enough data exists to update the guideline again. A list of upcoming guidelines can be found on cap.org.

REFERENCES

1. Wolff AC, Somerfield MR, Dowsett M, et al. Human epidermal growth factor receptor 2 testing in breast cancer: ASCO-CAP guideline update [published online June 7, 2023]. *Arch Pathol Lab Med.* 2023. doi:10.5858/arpa.2023-0950-SA