

Applying the 2023 ASCO-CAP guideline updates for **HER2** testing in breast cancer



Introduction

HER2 expression in breast cancer is currently categorized as HER2-negative and HER2-positive.¹ HER2-negative breast cancer makes up 85% of all cases.¹ However, 60% of HER2-negative breast cancers can show low levels of HER2 expression.^{1,2} Defined as HER2 IHC 1+ or IHC 2+ with negative ISH, these tumors are often referred to as HER2-low, and classed as a subset of HER2-negative breast cancers.¹

From their first publication in 2007, ASCO-CAP guidelines for HER2 testing in breast cancer have been a source of best practice guidance aimed at standardizing HER2 testing across pathology laboratories.³ Over the years, the guidelines have evolved to keep up with the changing HER2 landscape to ensure clinical care teams are well equipped to make optimal care decisions.³ In 2023, ASCO-CAP published a guideline update with a specific focus on recognizing and reporting HER2 IHC 1+ or IHC 2+/ISH- (HER2-low) tumors.⁴

Although HER2-low is not a distinct subtype of breast cancer, it is a clinically meaningful classification of HER2 expression.⁵ Identifying HER2-low tumors may have an impact on patient care; hence, the importance of standardizing assessment of low levels of HER2 expression has been recognized in the

most recent guideline updates.^{4,6} Consistent assessment of HER2-low cases, as well as clear reporting of results in the pathology report, can support physicians in making appropriate clinical decisions.

Special training is advised for pathologists to implement guideline updates in practice.^{7,8} However, this can be challenging considering access to quality training resources can vary between laboratories.^{9,10} Online educational platforms, such as HER2Know.com, provide access to a range of educational materials to help pathologists implement best practice recommendations for assessing low levels of HER2 expression. Freely accessible, HER2Know.com aims to provide information and case reviews for pathologists wanting to expand their knowledge of HER2-low assessment.

Summary of the updates and best practice recommendations

While the most recent updates affirmed the 2018 ASCO-CAP guideline recommendations on HER2 testing in breast cancer; they also offer best practices for differentiating HER2 IHC 0 and 1+ tumors and additional guidance around reporting HER2 IHC 1+, IHC 2+/ISH- results.⁴

Key best practice recommendations from the 2023 ASCO-CAP guideline updates



Test ordering

- All newly diagnosed patients with breast cancer must have a HER2 test performed⁴
- Patients who then develop metastatic disease must have a HER2 test performed in a metastatic site, if tissue sample is available⁴



Pre-analytic considerations

- Pay careful attention to pre-analytic conditions and follow guidelines for optimal tissue handling requirements⁴



Interpretation

- Use controls with a range of HER2 expression, including with HER2 IHC 1+ staining⁴
- Examine HER2 IHC at 40X magnification when distinguishing between HER2 IHC 0 from 1+ staining⁴



Second opinion

- Consider second pathologist review when results are close to the 0 versus 1+ interpretive threshold⁴



Reporting

- Always report semiquantitative (discrete) HER2 IHC scores⁴
- Include a footnote in the pathology report on the therapeutic implications of the results⁴



Considering previous results

- Medical oncologists can also consider historical HER2 IHC results (from prior or concurrent primary samples, or other metastatic sites) as there may be heterogeneity in HER2 expression levels between samples, and/or metastatic cancer tissue samples may suffer from pre-analytic conditions that are better monitored in primary breast tissue samples⁴

Implementing recommendations for interpreting HER2-low

Distinguishing between HER2 IHC 0 and IHC 1+ staining patterns can make a difference between reporting a tumor as HER2 IHC 0 or HER2-low (IHC 1+ or IHC 2+/ISH-).⁴ The importance of consistent scoring at this interpretative threshold is underlined in the 2023 ASCO-CAP guideline updates.⁴

- ASCO-CAP recommends using controls with a range of HER2 expression as well as 40X magnification in order to appreciate subtle staining patterns at the low end of the HER2 IHC spectrum⁴
- Seeking a second opinion is advised to increase reliability of results when distinguishing between HER2 IHC 0 and 1+.⁴ Approaches for consulting a second pathologist can vary in different laboratories and may depend on the size and available resources; it will be up to the clinical care team to establish the best course of action



“For borderline cases, pathologists may consider reaching internal consensus for a final HER2 score. As there are often inter-laboratory variations with HER2 IHC assays, in-house pathologists will be more familiar with the specific performance characteristics of the HER2 IHC assay used in their laboratory and may be more knowledgeable in the staining pattern of the HER2 antibody, and in discerning artifact or laboratory-specific features from that assay. Moreover, internal consensus will provide a faster turnaround time and promote consistency within the group.”

Dr. Shi Wei

How to report HER2-low and ensure the clinical care team recognizes its importance

Reporting practices for HER2-low results were emphasized in the recent guideline updates.⁴ ASCO-CAP guidelines and CAP template both recommend including semi-quantitative HER2 IHC scores in the pathology report: HER2 IHC 0, 1+, 2+, or 3+.^{4,6} It may also be considered to report intensity, pattern of staining, and percentage of cell staining along with the IHC score to provide a detailed description of the result.¹¹

For reporting HER2 IHC 1+, IHC 2+/ISH- results, ASCO-CAP recommends including a footnote in the pathology report which could aid communication between the pathologist and the clinical care team.⁴ Highlighting the most significant information in the pathology report can help ensure treating physicians have a clear understanding of details that affect

decisions about patient care. Although ASCO-CAP currently suggests it is premature to use the term ‘HER2-low’ in the report, the CAP reporting template acknowledges its value in their suggested template.⁶



“At my institution, we report both IHC scores and HER2 category (HER2-positive or HER2-negative). The term ‘HER2-low’ has not been used in our pathology reports yet; the 2023 ASCO-CAP guideline update suggests that pathologists use a new HER2 testing reporting comment to highlight the current relevance of IHC 0 versus 1+ results. In this regard, the new addition of ‘HER2-low’ in the CAP biomarker synoptic template facilitates the identification of these patients [patients with HER2-low breast cancer] readily, especially for the treating oncologists.”

Dr. Shi Wei

Conclusion

The changes in the HER2 landscape within breast cancer have highlighted the value of HER2-low classification. Recognizing HER2-low tumors can have clinical implications, and so it is important to standardize assessment of tumors with low levels of HER2 expression.

Implementing changes recommended by the most recent 2023 ASCO-CAP guideline updates can help ensure consistency in the assessment of HER2-low tumors. Although the updates cover specific guidance around pre-analytical variables, interpretation of borderline HER2 IHC 0 or 1+ cases, and reporting HER2 IHC 1+, IHC 2+/ISH- results, the way that they are adapted in practice may differ for each pathology laboratory and may require a discussion with the clinical care team.⁴

In order to adapt to the changing practices around HER2-low, it is suggested that pathologists should engage with educational content, whether it is visual aids, lectures, web-based training, or reviews of challenging case.⁸ HER2Know.com can support pathologists in evolving their clinical practice by providing peer-led educational resources for assessing HER2 IHC at the low end of the spectrum; it also provides a collection of clinical cases for pathologists to refine their scoring practice, such as borderline HER2 IHC 0 or 1+ cases.



Visit [HER2Know.com](https://www.her2know.com) and start exploring the resources today.

HER2Know

ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization.

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