CADTH Provisional Funding Algorithm

Pathology Implementation Advice Panel: Guidance for Reporting Diagnostic Classifications for Breast Cancer

Guidance

Abbreviations

ASCO	American Society of Clinical Oncology
CAP	College of American Pathologists
CAPCA	Canadian Association of Provincial Cancer Agencies
CPQA-AQCP	Canadian Pathology Quality Assurance – Assurance qualité canadienne en pathologie
ER	estrogen receptor
FISH	fluorescence in situ hybridization
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IHC	immunohistochemistry
PAG	Provincial Advisory Group
pCPA	pan-Canadian Pharmaceutical Alliance
PR	progesterone receptor

Key Messages

- The way estrogen receptor and progesterone receptor (ER/PR) scores are reported across jurisdictions in Canada may affect how patients with breast cancer are treated.
- A panel of pathologists convened to provide guidance and clarity on implementation issues related to ER/PR and human epidermal growth factor receptor 2 (HER2) testing and reporting that may impact drug eligibility for breast cancer treatment in Canada.
- The panel reached a consensus on matters related to ER/PR and HER2 testing for breast cancer, reporting hormone receptor results, the interpretation of results potentially indicative of triple-negative breast cancer, quality assurance, managing and reviewing historical cases, multiple metastatic sites, and multifocal sites.
- Readers should consider this advice in conjunction with the Breast Cancer Provisional Funding Algorithm and related drug funding decisions.

Background

The American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP) guidelines[1,2] define triple-negative breast cancer as less than a 1% expression of estrogen receptor (ER) and progesterone receptor (PR) as determined by immunohistochemistry (IHC), by either:

- a score of 0 or 1+ by IHC, or
- a score of 2+ by IHC and fluorescence in situ hybridization (FISH)-negative (not amplified) for human epidermal growth factor receptor 2 (HER2).

At recent Provincial Advisory Group (PAG) meetings and discussions, members indicated that there may be jurisdictional differences in how ER and PR scores are reported. Additionally, the CADTH pan-Canadian Oncology Drug Review Expert Review Committee's recommendation of trastuzumab deruxtecan for HER2-low metastatic breast cancer endorsed the pathologist recommendation that archival (i.e., before 2022) HER2 IHC 0 samples be reread, as this could identify patients who would be eligible for trastuzumab deruxtecan.

At the request of CADTH's jurisdictional advisory committee for oncology drugs (i.e., PAG), CADTH convened a pan-Canadian Implementation Advice Panel of pathologists (September 8, 2023). This panel provided advice for the following implementation question:

- How should the new diagnostic classifications, hormone receptor (HR)-low (i.e., ER/PR scores of 1% to 10% as low-level) and HER2-low, be consistently tested and reported?

The harmonization between this pathology panel and the Provisional Funding Algorithm Panel was crucial to effectively discuss treatment strategies for breast cancer.

To establish a pan-Canadian pathology panel, the Canadian Association of Provincial Cancer Agencies (CAPCA) assisted with identifying pathologists. Prior to the pathology panel meeting, CADTH conducted an

informal, online survey with PAG members to obtain context from the jurisdictions about the implementation issues related to ER/PR and HER2 testing and reporting that may impact drug eligibility. The results from the PAG survey were compiled, summarized, and shared with the expert pathology panellists as part of the orientation meeting materials.

Objective of the Panel

The objective is to provide guidance and clarity on implementation issues related to ER/PR and HER2 testing and reporting that may impact drug eligibility from the clinical perspectives of pathologists practising across Canada.

Consultation Process and Objective

The Implementation Advice Panel comprised 7 pathologists with expert knowledge of and clinical experience with breast cancer, including related testing and reporting guidelines; 1 medical oncologist who prompted additional questions that were anticipated to inform the Provisional Funding Algorithm Panel; and a panel chair. One additional pathologist submitted their responses to the discussion questions via email, which was considered during the panel when developing their advice. Overall, the panel included clinicians from 7 provinces: British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, and Nova Scotia.

The panel's objective was to provide expert advice and clarity on implementation issues related to ER/PR and HER2 testing and reporting that may impact drug eligibility. This advice was used by the Provisional Funding Algorithm Panel tasked with advising the participating drug programs regarding the funding algorithm and any related implementation questions.

The panel members, key CADTH staff, and the chair attended the meeting. The panel used a consensus-based approach to guide discussions addressing the implementation question.

Following the panel meeting, CADTH staff prepared a summary of the panel's input. Additional input from the panellists informed the final document. CADTH staff posted the draft report on CADTH's website for stakeholder feedback; however, CADTH did not receive any additional feedback. The implementation panel members developed the advice provided in this report from their knowledge and expertise, and it reflects opinions informed by the panellists' experiences, which may not necessarily be based on published evidence from clinical trials.

Focus of Report

This report is based on the panel's discussion, which centred around how the new diagnostic classifications, HR-low and HER2-low, are being tested and reported in Canada.

Summary of Implementation Advice

On behalf of the Pathology Panel, we provide recommendations that may help inform the Breast Cancer Provisional Funding Algorithm Panel and related drug funding decisions.

The panellists reached consensus for the following statements:

All jurisdictions should follow the current ASCO/CAP clinical practice guidelines when reporting ER/PR and HER2 testing for breast cancer.

- This recommendation has a strong caveat that it must be considered with the subsequent statements to support the nuances of this field (e.g., analytical sensitivity of different assays used across Canada, and patient management of PR-low, which is currently not described in ASCO/CAP guidelines[1]) and allow for clinical judgment.
- The ASCO/CAP guidelines[1,2] are the gold standard and followed worldwide, and there is no other predominant guideline for this topic. Updates in definitions will vary in frequency. Some definitions are updated regularly (i.e., HER2)[2] while others change infrequently (i.e., ER/PR).[1] The evolution of precision medicine may require more frequent changes. While the definitions of categories may remain unchanged, how individuals use these categories will evolve.
- Additional context: One panel member stated that changes in HER2 status occurred in the 2007, 2014, and 2018 ASCO/CAP guidelines. The 2023 HER2 update[2] does not support a new category of HER2-low, but stresses the need for reporting HER2 IHC score; ER/PR status interpretation was set at greater than 1% in 2010, and it was only in 2020 that the ER-low category was introduced.

For HR results, reports should include category (i.e., positive, low-positive, or negative for ER; positive or negative for PR) and reported data elements (i.e., percentage [either an exact value or range] of cell staining and intensity) to allow for clinical judgment by medical oncologists for patient management.

- A panellist emphasized that all laboratories and pathologists should be encouraged to report according to ASCO/CAP guidelines and to use synoptic reporting for this purpose according to the CAP template.[3] The panellists believe most jurisdictions are adhering to this recommendation, but there is still some variability between provinces. For example:
  - The panellist noted that "ER low-positive" may not be stated in all reports in that province, but data elements are all usually described somewhere in the synoptic report.
  - One panellist stated that their current report format includes a disclaimer that they only report ER as positive or negative, but it is believed that pathologists in their jurisdiction have been reporting using the 3 recommended categories for ER in the final diagnosis line.

- A panel member emphasized that synoptic reporting is the best way to standardize reporting breast biomarker results.
- For ER low-positive results, current ASCO/CAP guidelines[1] recommend reports include the following comment: "The cancer in this sample has a low level (1%-10%) of ER expression by IHC. There are limited data on the overall benefit of endocrine therapies for patients with these results, but they currently suggest possible benefit, so patients are considered eligible for endocrine treatment. There are data that suggest invasive cancers with these results are heterogeneous in both behavior and biology and often have gene expression profiles more similar to ER-negative cancers." To extend beyond this, the panel suggests medical oncologists be empowered to use clinical judgment, as ER-low patients may be ineligible for triple-negative therapy or clinical trials.
- Moreover, if using the Allred scoring system, it should be used in addition to reporting category and reported data elements.
    - Panellists from 3 jurisdictions reported using the Allred scoring system in addition to reporting category and reported data elements. One panellist from another jurisdiction stated that they do not usually report based on the Allred scoring system.
        - Additional context: One panellist stated their standard is to report Allred score and its components (percent category 0 to 5 [0 = none, 1 = less than 1%, 2 = 1% to 10%, 3 = 11% to 33%, 4 = 34% to 66%, 5 = 67% to 100%] and intensity score 0 to 3). They mentioned that they do not report a specific percent of cell staining, even when in the 1% to 10% range. Importantly, the ER result categorization of negative, low-positive, or positive is based solely on percent cells staining less than 1%, 1% to 10%, or greater than 10% as per ASCO/CAP guidelines, not the Allred score (i.e., Allred 3 and 4 will be reported as negative if < 1% of cells are staining with moderate or strong intensity; and ER low-positive can be Allred 3, 4, or 5 when 1% to 10% of cells stain with low, moderate, or strong intensity, respectively).
    - Note: The current ASCO/CAP guidelines[1] did not include reporting Allred scores (i.e., this was removed from a previous iteration).

The definition of triple-negative breast cancer should be aligned with ASCO/CAP guidelines; however, given differences in assay sensitivities and lack of clinical evidence regarding the behaviour of certain categories (i.e., ER-negative or PR-positive; ER-low or PR-negative), the pathology panel supports oncologist interpretation of some low-positive results for ER and PR as negative.

- The current definition for triple-negative breast cancer is a less than 1% expression of ER/PR by IHC by either a score of 0 or 1+ by IHC; or a score of 2+ by IHC and FISH-negative (not amplified) for HER2.[1,2]
- Thanks to advanced technology, this is a new era for testing. Improvements in analytical sensitivities and levels of amplification are causing some samples, previously reported as negative, to now be reported as positive. One panellist commented that there is variability in analytical sensitivity that may result in different rates of ER-low. Another panellist also reported that the thresholds for

positivity have been lowered over time (e.g., previous thresholds to report ER-positive were 10%, and are now 1%) because of increased sensitivity of IHC assays to detect ER.

- Two example cases were presented by the medical oncologist in attendance:
  - **Is ER-negative, PR-low, HER2-negative considered triple-negative breast cancer?**
    - Panellists acknowledged that this is a difficult question.
    - One panellist stated that the tumour group considers tumours that have ER/PR levels of 1% to 10% to be HR-negative, and these cases are functionally like triple-negative cases.
    - Another panellist mentioned that they would check controls and repeat the PR testing in that setting for confirmation.
    - An additional panellist stated that there is a lack of published evidence: as per indirect evidence, low PR and low ER can be found in other sites, such as in lung cancer. Low PR is not HR-positive disease.
    - Further, another panellist suggested that a clinical trial comparing ER-negative (< 1%) versus ER-low may be the way to answer the question.
  - **How should patients with ER-negative, PR-positive, HER2-negative scores be treated?**
    - Panellists responded that while this case has low PR positivity, there is insufficient evidence that such patients benefit from hormone therapy and should be considered HR-negative.

The sensitivity of the immunoassay used will have an impact on the result, and therefore the eligibility to access triple-negative breast cancer treatments for some patients. The panel acknowledges the importance of advocating for clinical decision-making for appropriate patient management.

- Panellists discussed challenges with some of the analytical sensitivities of the different assays currently used across Canada.[4] Analytical sensitivity of the laboratory-developed tests for ER, PR, and HER2 is not standardized or harmonized across different laboratories in Canada, irrespective of their location and/or level of expertise.
- Results from the first round of proficiency testing aimed at HER2-low offered through Canadian Pathology Quality Assurance – Assurance qualité canadienne en pathologie (CPQA-AQCP) showed that most participating labs demonstrated excellent sensitivity compared to the reference FDA-approved clinical trial assay, but many labs showed poor specificity (i.e., identified a larger proportion of 1+ cases, which were scored as 0 by the clinical trial assay).[5]
- Panellists recognized that some of currently used laboratory-developed tests may be too sensitive and are producing false-positive results, which is particularly pertinent for ER and PR, while other laboratory-developed tests may have too low sensitivity and are reporting false-negative results, the which is especially relevant for HER2.
- The panel also acknowledged that there will likely never be centralization of assay types. A short-term solution may be communication, ensuring that medical oncologists are aware of which assay is being used in their laboratory and its analytical sensitivity (e.g., using reference materials to check controls and know where their assay sensitivity stands). A longer-term solution may be improved compliance

with quality assurance programs, potentially providing laboratories with the tools to measure their own analytical sensitivity. The panel discussed the suggestion of implementing mandatory centralized national proficiency testing to harmonize sensitivity and specificity between ER-positive and ER-negative, as well as HER2-negative and HER2-low, but concluded that it was out of scope for this discussion.

- The medical oncologist asked, "Many of these decisions are made in core biopsies for neoadjuvant treatment. Is there any consideration that is different for that?" One panellist responded, "We apply the same guidelines to core or resection specimen; a neoadjuvant setting, we repeat them on the excision and sometimes we repeat if there are certain criteria on a resection specimen as well (changing grade low amount of tumour on the core, etc.)."

For managing historical cases with previously reported HER2 scores by IHC as 0 or 1+ before 2022, the pathology panel suggests that reviewing and/or retesting should be oncologist-driven.

- The members of the panel all agreed on reviewing or retesting HER2 (upon request by oncologists) that was previously reported before 2022 by IHC as 0, but an IHC value of 1+ was not as definitive (differences in laboratories across Canada, assay sensitivities, and other considerations were all discussed, further highlighting that clinical judgment is necessary). Assays and sensitivities have changed, and if retested, some cases previously reported as HER2 IHC 0 could now be classified as 1+. The recent seminal publication regarding a randomized clinical trial, DESTINY-Breast04,[6] found that targeting HER2 can provide clinically meaningful benefits for patients with HER2-low metastatic breast cancer. These findings added clinical importance in differentiating between 0 and 1+, as they may result in different treatment and care pathways.

For all patients with multiple metastatic sites with differing biomarker results, consultation between oncology and pathology is encouraged. Treatment recommendations should be based on the best available evidence and clinical judgment.

- This statement is intentionally nuanced and not overly prescriptive to protect uncommon cases that may require clinical judgment from pathologists and/or oncologists. This is to ensure patients do not miss potential treatments because of a technicality versus an informed, expert clinical decision. The panellists are cognizant that there may not be evidence-based research for every scenario, especially with advanced disease.

At the pathologist's discretion, for patients with multifocal or multicentric disease: biomarker testing does not need to be performed on smaller foci if morphologically similar to the largest tested focus (this includes triple-negative breast cancer); and biomarker testing may be necessary on separate foci if the morphology looks different.

References

1. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. *J Clin Oncol.* 2020;38(12):1346-1366. PubMed
2. Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *Arch Pathol Lab Med.* 2018;142(11):1364-1382. PubMed
3. Fitzgibbons P, Connolly J. Template for reporting results of biomarker testing of specimens from patients with carcinoma of the breast. Version 1.5.0.1. Northfield (IL): College of American Pathologists; 2023: https://documents.cap.org/documents/Breast.Bmk_1.5.0.1.REL_CAPCP.pdf. Accessed 2023 Nov 9.
4. Torlakovic EE, Sompuram SR, Vani K, et al. Development and validation of measurement traceability for in situ immunoassays. *Clin Chem.* 2021;67(5):763-771. PubMed
5. Summary Report – Run 186 HER2-low. Richmond (BC): Canadian Pathology Quality Assurance (CPQA); 2023 Feb: https://cpqa.ca/assessments/Run%20186%20HER2-low%20summary.pdf. Accessed 2023 Nov 9.
6. Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan (T-DXd) versus treatment of physician's choice (TPC) in patients (pts) with HER2-low unresectable and/or metastatic breast cancer (mBC): Results of DESTINY-Breast04, a randomized, phase 3 study. Meeting abstract from: 2022 ASCO Annual Meeting II, 2022 Jun 3-7, Chicago (IL). *J Clin Oncol.* 2022;40(17_suppl):LBA3-LBA3.

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