ASCO Guidelines

COLLEGE of AMERICAN PATHOLOGISTS

Estrogen and Progesterone Receptor Testing in Breast Cancer: 2020 Guideline Update

Statements and Strengths of Recommendations

SUMMARY OF RECOMMENDATIONS

Guideline Statement	Strength of Recommendation
Recommendation 1.1. Optimal algorithm for estrogen (ER)/ progesterone (PgR) testing Samples with 1-100% of tumor nuclei positive for ER or PgR are interpreted as positive. For reporting of ER (not PgR), if 1-10% of tumor cell nuclei are immunoreactive, the sample should be reported as ER Low Positive with a recommended comment* (see manuscript Table 2; Figure 1). A sample is considered negative for ER or PgR if <1% or 0% of tumor cell nuclei are immunoreactive. A sample may be deemed uninterpretable for ER or PgR if the sample is inadequate (insufficient cancer or severe artifacts present, as determined at the discretion of the pathologist), if external and internal controls (if present) do not stain appropriately, or if pre-analytic variables have interfered with the assay's accuracy (see manuscript Figures 1-4). Clinicians should be aware of and able to discuss with patients the limited data on ER Low Positive cases and issues with test results that are close to a positive threshold. *Recommended comment for 1-10% cells staining: 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 low level (1-10%) ER expression 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. Recommended comment when no internal controls and ER is 0-10%: No internal controls are present, but external controls are appropriately positive. If needed, testing another specimen that contains internal controls may be warranted for confirmation of ER status.	Strong
Recommendation 1.2. Optimal testing conditions Large (preferably multiple) core biopsies of tumor are preferred for testing if they are representative of the tumor (grade and type) at resection. Accession slip and report must include guideline-detailed elements.	Strong

Recommendation 1.3. Optimal tissue handling requirements Time from tissue acquisition to fixation should be as short as possible. Samples for ER and PgR testing are fixed in 10% neutral buffered formalin (NBF) for 6 to 72 hours. Samples should be sliced at 5-mm intervals after appropriate gross inspection and margin designation and placed in sufficient volume of NBF to allow adequate tissue penetration. If tumor comes from remote location, it should be bisected through the tumor on removal and sent to the laboratory immersed in a sufficient volume of NBF. Cold ischemia time, fixative type, and time the sample was placed in NBF must be recorded. As in the ASCO/CAP HER2 guideline, using unstained slides cut more than 6 weeks before analysis is not recommended. Time tissue is removed from patient, time tissue is placed in fixative, duration of fixation, and fixative type must be recorded and noted on accession slip or in report.	Strong
Recommendation 1.4. Optimal internal validation procedures This topic is deferred to the forthcoming CAP guideline update of the principles of analytic validation of immunohistochemical (IHC) assays, once available. There should be initial test validation/verification prior to reporting any clinical samples. Prior to that, previously recommended principles apply (see Fitzgibbons et al[2] and more recently Torlakovic[3]).	Strong
Recommendation 1.5. Optimal internal QA procedures Ongoing quality control and equipment maintenance are required. Initial and ongoing laboratory personnel training and competency assessment should be performed. Standardized operating procedures (SOPs) should be used that include routine use of external control materials with each batch of testing and routine evaluation of internal normal epithelial elements or the inclusion of normal breast sections (or other appropriate control) on each tested slide, wherever possible. External controls should include negative and positive samples as well as samples with lower percentages of ER expression (such as tonsil). On-slide controls are recommended. Regular, ongoing assay reassessment should be done at least semiannually (as described in Fitzgibbons et al[2]). Revalidation is needed whenever there is a significant change to the test system.[3] Ongoing competency assessment and education of pathologists are required.	Strong
Recommendation 1.6. Optimal external proficiency assessment The laboratory performing ER and PgR testing must participate in external proficiency testing or alternative performance assessment as required by its accrediting organization.	Strong
Recommendation 1.7. Optimal laboratory accreditation On-site inspection every other year should be undertaken with annual requirement for self-inspection.	Moderate
Recommendation 2.1. Laboratories should include ongoing quality control using SOPs for test evaluation prior to scoring (readout) and interpretation of any case as defined in the checklist in manuscript Figure 1.	Strong
Recommendation 2.2. Interpretation of any ER result should include evaluation of the concordance with the histologic findings of each case. Clinicians should also be aware of when results are highly unusual/discordant and work with pathologists to attempt to resolve or explain atypical reported findings. (See manuscript Table 3 as an aid in this process.)	Strong
Recommendation 2.3. Laboratories should establish and follow an SOP stating the steps the laboratory takes to confirm or adjudicate ER results for cases with weak stain intensity or $\leq$10% of cells staining (see Supplemental Digital Content Data Supplement 2, Figure 1 for an example SOP).	Strong

Recommendation 2.4. The status of internal controls should be reported for cases with 0-10% staining. For cases with these results without internal controls present and with positive external controls, an additional report comment is recommended (see manuscript Table 2).	Strong
Recommendation 3. Validated IHC is the recommended standard test for predicting benefit from endocrine therapy. No other assay types are recommended as the primary screening test for this purpose.	Strong
Recommendation 4. ER testing in cases of newly diagnosed ductal carcinoma in situ (DCIS) (without associated invasion) is recommended to determine potential benefit of endocrine therapies to reduce risk of future breast cancer. PgR testing is considered optional.	Moderate

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation

References

1. Allison KH, Hammond EH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists guideline update. *Arch Pathol Lab Med*. 2020;144(5):545–563. doi:10.5858/arpa.2019-0904-SA

2. Fitzgibbons PL, Murphy DA, Hammond ME, et al: Recommendations for validating estrogen and progesterone receptor immunohistochemistry assays. *Arch Pathol Lab Med.* 134:930-5, 2010

3. Torlakovic EE, Cheung CC, D'Arrigo C, et al: Evolution of Quality Assurance for Clinical Immunohistochemistry in the Era of Precision Medicine. Part 3: Technical Validation of Immunohistochemistry (IHC) Assays in Clinical IHC Laboratories. *Appl Immunohistochem Mol Morphol* 25:151-159, 2017

4. American Society of Clinical Oncology. ASCO® Guidelines Methodology Manual. https://www.asco.org/sites/new-www.asco.org/files/content-files/practice-and-guidelines/documents/2019-Guidelines-Methodology-Manual.pdf. Accessed December 31, 2019.