ASCO Guidelines

COLLEGE of AMERICAN PATHOLOGISTS

Estrogen and Progesterone Receptor Testing in Breast Cancer: Guideline Update

Original Recommendations vs Guideline Update

2010 RECOMMENDATIONS	UPDATED RECOMMENDATIONS
Clinical Question 1. What are the optimum quality assurance (QA), tissue handling, scoring system, and reporting for determining potential benefit from endocrine therapy?	
Optimal algorithm for ER/PgR testing Positive for ER or PgR if finding of ≥1% of tumor cell nuclei are immunoreactive. Negative for ER or PgR if finding of <1% of tumor cell nuclei are immunoreactive in the presence of evidence that the sample can express ER or PgR (positive intrinsic controls are seen). Uninterpretable for ER or PgR if finding that no tumor nuclei are immunoreactive and that internal epithelial elements present in the sample or separately submitted from the same sample lack any nuclear staining.	**Recommendation 1.1. Optimal algorithm for ER/PgR testing (updated, strong recommendation)** 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 preanalytic 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.
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. cession slip and report must include guideline-detailed elements.	**Recommendation 1.2. Optimal testing conditions (no change, strong recommendation)** 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.

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% NBF for 6 to 72 hours. Samples should be sliced at 5-mm intervals after appropriate gross inspection and margins designation and placed in sufficient volume of neutral buffered formalin (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, use of 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.	**Recommendation 1.3. Optimal tissue handling requirements (no change, strong recommendation)** Time from tissue acquisition to fixation should be as short as possible. Samples for ER and PgR testing are fixed in 10% NBF for 6 to 72 hours. Samples should be sliced at 5-mm intervals after appropriate gross inspection and margins 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, use of 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.
Optimal internal validation procedures Internal validation must be done before test is offered; see separate article on testing validation (Fitzgibbons et al[2]). Validation must be done using a clinically validated ER or PgR test method. Revalidation should be done whenever there is a significant change to the test system, such as a change in the primary antibody clone or introduction of new antigen retrieval or detection systems.	**Recommendation 1.4. Optimal internal validation procedures (change anticipated, strong recommendation)** This topic is deferred to the forthcoming CAP guideline update, 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]).
Optimal internal QA procedures Ongoing quality control and equipment maintenance. Initial and ongoing laboratory personnel training and competency assessment. Use of standard operating procedures (SOPs), including 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 on each tested slide, wherever possible. Regular, ongoing assay reassessment should be done at least semiannually (as described in Fitzgibbons et al[2] and more recently Torlakovic[3]); revalidation is needed whenever there is a significant change to the test system. Ongoing competency assessment and education of pathologists.	**Recommendation 1.5. Optimal internal QA procedures (updated, strong recommendation)** Ongoing quality control and equipment maintenance are required. Initial and ongoing laboratory personnel training and competency assessment should be performed. 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 is required.

Optimal external proficiency assessment Mandatory participation in external proficiency testing program with at least two testing events (mailings) per year. Satisfactory performance requires at least 90% correct responses on graded challenges for either test.	**Recommendation 1.6. Optimal external proficiency assessment (updated, strong recommendation)** The laboratory performing ER and PgR testing must participate in external proficiency testing or alternative performance assessment as required by its accrediting organization.
Optimal laboratory accreditation On-site inspection every other year with annual requirement for self-inspection.	**Recommendation 1.7. Optimal laboratory accreditation (no change, moderate recommendation)** On-site inspection every other year should be undertaken with annual requirement for self-inspection.
Clinical Question 2. What additional strategies can promote optimal performance, interpretation, and reporting of IHC assays, particularly in cases with low ER expression?	
No specific recommendations were specified in 2010 for low ER expression cases.	**Recommendation 2.1. (updated, strong recommendation)** 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. **Recommendation 2.2. (updated, strong recommendation)** 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). **Recommendation 2.3. (updated, strong recommendation)** 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). **Recommendation 2.4. (updated, strong recommendation)** 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).
Clinical Question 3. Are other ER expression assays acceptable for identifying patients likely to benefit from endocrine therapy?	
No assays other than IHC are recommended as testing platforms.	**Recommendation 3. (updated, strong recommendation)** 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.

Clinical Question 4. Should ductal carcinoma in situ (DCIS) be routinely tested for hormone receptors?	
ER and PgR testing of DCIS is optional (no formal recommendation made to test or not test).	**Recommendation 4. (updated, moderate recommendation)** ER testing in cases of newly diagnosed 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.

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.