

This requirement is applicable to both new and existing assays. If review of the initial validation/verification does not meet the current standard, it must be supplemented and brought into compliance. If no records exist from the initial validation/verification, the assay must be fully revalidated/verified.

Evidence of Compliance:

- ✓ Records of validation/verification data including criteria for concordance

REFERENCES

- 1) Wolff AC, Somerfield MR, Dowsett M, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Guideline Update. *Arch Pathol Lab Med*. Published online June 7, 2023. doi: 10.5858/arpa.2023-0905-SA.
- 2) Fitzgibbons PL, Murphy DA, Hammond ME, Allred DC, Valenstein P. Recommendations for validating estrogen and progesterone receptor immunohistochemistry assays. *Arch Pathol Lab Med* 2010; 134:930-935.
- 3) Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer; American Society of Clinical Oncology/College of American Pathologists. *Arch Pathol Lab Med* 2014;138(2):241-256
- 4) Goldsmith JD, Troxell M, Roy-Chowdhuri S, et al. Principles of analytic validation of immunohistochemical assays: guideline update. *Arch Pathol Lab Med*. 2024. <https://doi.org/10.5858/arpa.2023-0483-CP>

CYP.04540 Estrogen Receptor and HER2 Testing in Breast Cancer Samples

Phase I



At least one tumor sample from all patients with invasive breast cancer (newly diagnosed, recurrent, or metastatic disease) is tested for estrogen receptors and HER2 (by IHC or ISH) if tissue is available.

REFERENCES

- 1) Wolff AC, Somerfield MR, Dowsett M, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Guideline Update. *Arch Pathol Lab Med*. Published online June 7, 2023. doi: 10.5858/arpa.2023-0905-SA.

CYP.04550 Fixation - HER2 and ER Breast Cancer Predictive Marker Testing

Phase I



If the laboratory assesses HER2 protein over-expression by immunocytochemistry, or estrogen receptor expression by immunocytochemistry for breast cancer predictive marker testing, the laboratory monitors cold ischemia time (one hour or less), if applicable, and appropriate specimen fixation time.

NOTE: The CAP strongly recommends that specimens subject to these tests be fixed in 10% neutral buffered formalin for at least six hours and up to 72 hours at room temperature. Specimens must be fully submerged in the optimal volume of formalin to achieve a formalin to specimen volume of 10:1 or higher, or if not feasible (eg, large specimens) at least 4:1. For cases with negative HER2 results by immunocytochemistry that were fixed outside these limits, confirmatory analysis by in situ hybridization is strongly recommended.

Both the time of removal of the tissue and the time of immersion of the tissue in fixative must be recorded and communicated from the submitting service to the processing laboratory.

Communication to clinical services of the need for appropriate information on cold ischemia time, fixative, and fixation time may be through memoranda, website, phone, face-to-face meetings, or other means. Information about fixative, fixation time, and cold ischemia time (if applicable) for each specimen must be recorded as part of the permanent specimen record in the pathology report. The laboratory must monitor for compliance and take corrective action as needed.

If specimens are fixed in a solution other than 10% neutral buffered formalin, the laboratory must perform a validation study showing that HER2 and ER results are concordant with results from formalin-fixed tissues.

Laboratories testing specimens obtained from another institution must have a policy that addresses cold ischemia time (if applicable) and time of fixation. Information on time of fixation may be obtained by appropriate questions on the laboratory's requisition form. If specimens have undergone any deviation from processing that may interfere with result interpretation, this must be annotated on the final report.

Evidence of Compliance:

- ✓ Records of communication of cold ischemia (if applicable) and fixation guidelines to clinical services **AND**
- ✓ Records of action taken when cold ischemia (if applicable) and fixation times are consistently outside of required parameters or are not available to the laboratory

REFERENCES

- 1) Wolff AC, Somerfield MR, Dowsett M, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Guideline Update. *Arch Pathol Lab Med*. Published online June 7, 2023. doi: 10.5858/arpa.2023-0905-SA.
- 2) Compton CC, Robb JA, Anderson MW, et al. Preanalytics and Precision Pathology: Pathology Practices to Ensure Molecular Integrity of Cancer Patient Biospecimens for Precision Medicine. *Arch Pathol Lab Med*. 2019;143(11):1346-63.
- 3) 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):545-63.

ON-SITE MICROSCOPIC REVIEW

On-site review of actual case (slide) material and corresponding reports is an important element of the inspection process. This is NOT a comprehensive rescreening of slides or evaluation of competency, but rather an action to facilitate the Inspector's evaluation of the laboratory's overall procedures.

Laboratories that do not file slides on-site (for example, some "read-only" laboratories) must retain a sample of slides on-site for review by the inspector on all days when the laboratory is subject to its regular on-site inspection. The sample must, at minimum, include all slides accessioned over a continuous two-week period within the previous two years. The laboratory must be able to produce any slide upon the request of an inspector during the required retention period for gynecologic and non-gynecologic slides (including fine needle aspiration slides).

Inspector Instructions:

- Review a randomly selected representative sample of 10-15 cases using the table below to guide selection:

Gynecologic Cases	Non-Gynecologic Cases (including FNAs)
Unsatisfactory	Negative for malignancy / Reactive
Negative for intraepithelial lesion or malignancy (NILM) / Repair	Atypical or suspicious with qualifiers / Suspicious for malignancy / Positive for malignancy
Atypical squamous cells	
LSIL (encompassing HPV)	
HSIL / Carcinoma	
p16/Ki67 dual stain	

Cases should be selected by the laboratory pathologist and/or cytopathology supervisor in a random manner defined by the inspecting Team Leader (eg, the first 1-3 negative and abnormal cases in each specimen category from a certain date or week). The following are core elements of the on-site review:

- Evaluate slides for quality of technical preparation and specimen adequacy
- Determine if significant cells have been identified
- Compare slides with the diagnostic report for completeness and clarity of diagnostic terminology
- Determine if the information provided with the requisition and included in the diagnostic report is complete and appropriate