Step 1: Checklist for quality control:

- Test performed using validated methodology with ongoing monitoring
- Evaluating pathologist trained in interpretation according to guidelines with ongoing competency assessment (per laboratory SOP)
- External controls (batch, on slide) stained appropriately
- Sample tested considered adequate (sufficient invasive cancer present for interpretation [or DCIS, if appropriate], free of major artifacts)
- Pre-analytical variables documented (formalin fixation, time to fixation, time in fixation)*

Note: If any of the above factors cannot be confirmed test should not be interpreted until resolved

Step 2: Evaluate stain intensity and percent of cancer cells staining

- Intensity of stain weak^ OR ≤ 10% of cells staining
  - Evaluate internal controls
    - Internal controls stain appropriately
      - See Figure 2
    - No internal controls in sample tested
      - See Figure 3
    - Internal controls weaker than expected or negative
      - See Figure 4
  - Report as ER Positive

- Intensity of stain moderate-strong and > 10% of cells staining
  - If result considered concordant with histology

*If pre-analytical variables not documented (e.g. a referral test from areas with limited resources) test must be reported with comment that pre-analytical variables were not documented and therefore results may not be valid

^Weak stain intensity is only appreciated on high power (20x-40x).
Intensity of stain weak^ or ≤ 10% of cells staining and Internal controls stain appropriately

- No cells staining (0%)
- ≤ 10% of cells with any staining (<1% or 1-10%)
- >10% of cells staining (but weak)

If result considered concordant with histology

Report as ER Negative (report that 0% of cells stained positive and that internal positive controls were adequate)

Obtain a second review by another qualified pathologist or validated digital image analysis (if not initially performed) on percent of cells staining and adjudicate result

If result considered concordant with histology

Report as ER Positive (report % of sample staining positive and that internal positive controls were adequate)

<1% of cells staining

Report as ER Negative (<1%) with recommended comment* and that internal positive controls were adequate

1-10% of cells staining

Report as ER Positive (1-10%) with recommended comment** and % of cells staining. Include that internal positive controls were adequate

^Weak stain intensity is only appreciated on high power (20x-40x)

Report comments:

*Although rare cancer cells stain with ER, they are <1% of the total in the sample reviewed, which is therefore considered ER-negative. Testing of future samples should be considered if there is concern that ER expression may be heterogenous.

**There are limited data on the overall benefit of hormonal therapies for patients with cancers with low level (1-10%) ER expression. In this setting, it is reasonable for clinicians to discuss the pros and cons of endocrine therapy with patients whose tumors contain low levels of ER by IHC and to make an informed decision based on the balance. There is data that suggests high grade cancers with this low level of ER expression typically have gene expression and genetic profiles similar to ER negative cancers.
Intensity of stain weak\(^{\text{a}}\) or \(\leq 10\%\) of cells staining and NO internal controls stain in sample tested

- Is there another sample with internal controls available?
  - Yes: Run test on another sample that has internal controls (return to Step 1)
  - No: Did batch external controls work and all pre-analytic and analytic steps appropriate? Is result considered concordant with histology?
    - Yes: Interpret per Figure 2 but include additional reporting comment that no internal controls but external controls were appropriately positive.*
    - No: Possible issues identified
      - If preanalytic issue identified (e.g., >1 hour ischemic time), report as insufficient for testing OR report (per Figure 2) with additional comment that the result may be invalid. Recommend that an additional sample be obtained for testing.
      - If analytic issues identified (e.g., batch external controls did not work), troubleshoot assay and repeat test internally or at another lab.

\(^{\text{a}}\)Weak stain intensity is only appreciated on high power (20x-40x).

* No internal controls were present in this sample, however, external controls were appropriately positive. The results are reported with this limitation noted. Additional testing for ER on future samples with internal controls may be warranted for confirmation of ER status.
Intensity of stain weak^ or <10% of cells staining and Internal controls weaker than expected or negative

Repeat test on same sample

Controls now appropriate, follow figure 2

Controls remain weak or negative

Work-up of pre-analytical and analytical issues with case or batch

If preanalytic issue identified (e.g., >1 hour ischemic time) can report as insufficient for testing OR report (per Figure 2) with additional comment that the result may be invalid. Recommend that an additional sample be obtained for testing.

If analytic issues identified (ex. Batch controls did not work) troubleshoot assay and repeat test internally until resolved or perform at another lab.

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