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## Summary of ASCO/CAP HER2 Guideline Recommendations

### Optimal algorithm for HER2 testing

#### Recommendation:

Positive for HER2 is either IHC HER2 3+ (defined as uniform intense membrane staining of > 30% of invasive tumor cells) or FISH amplified (ratio of *HER2* to *CEP17* of >2.2 or average *HER2* gene copy number >six signals/nucleus for those test systems without an internal control probe).

Equivocal for HER2 is defined as either IHC 2+ or FISH ratio of 1.8–2.2 or average *HER2* gene copy number four to six signals/nucleus for test systems without an internal control probe.

Negative for HER2 is defined as either IHC 0-1+ or FISH ratio of <1.8 or average *HER2* gene copy number of <four signals/nucleus for test systems without an internal control probe.

#### Comments:

These definitions depend on laboratory documentation of the following:

1. Proof of initial testing validation in which positive and negative HER2 categories are 95% concordant with alternative validated method or same validated method for HER2.
2. Ongoing internal QA procedures.
3. Participation in external proficiency testing.
4. Current accreditation by valid accrediting agency.

### Optimal FISH testing requirements

#### Recommendation:

Fixation for fewer than 6 hours or longer than 48 hours is not recommended.

Test is rejected and repeated if:

- Controls are not as expected.
- Observer cannot find and count at least two areas of invasive tumor.
- >25% of signals are unscorable due to weak signals.
- >10% of signals occur over cytoplasm.
- Nuclear resolution is poor.
- Autofluorescence is strong.

Interpretation done by counting at least 20 cells; a pathologist must confirm that counting involved invasive tumor.

Sample is subjected to increased counting and/or repeated if equivocal; report must include guideline-detailed elements.

### Optimal IHC testing requirements

#### Recommendation:

Fixation for fewer than 6 hours or longer than 48 hours is not recommended.

Test is rejected and repeated or tested by FISH if:

- Controls are not as expected.
- Artifacts involve most of sample.
- Sample has strong membrane staining of normal breast ducts (internal controls).

Interpretation follows guideline recommendation.

- Positive HER2 result requires homogeneous, dark circumferential (chicken wire) pattern in >30% of invasive tumor.
- Interpreters have method to maintain consistency and competency.

Sample is subjected to confirmatory FISH testing if equivocal based on initial results.

Report must include guideline-detailed elements.

# Summary of ASCO/CAP HER2 Guideline Recommendations

## Optimal tissue handling requirements\*

\*Revised per the 2011 ASCO/CAP Clinical Notice on HER2 and ER/PgR

### Recommendation:

Time from tissue acquisition to fixation should be ≤ one hour; samples for HER2 testing are fixed in neutral buffered formalin (NBF) for 6–48 hours; samples should be sliced at 5–10mm intervals after appropriate gross inspection and margins designation and placed in sufficient volume of neutral buffered formalin. 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.

Sections should ideally not be used for HER2 testing if cut > 6 weeks earlier; this may vary with primary fixation for storage conditions.

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 procedure

### Recommendation:

Validation of test must be done before test is offered.

Initial test validation requires 25–100 samples tested by alternative validated method in the same laboratory or by validated method in another laboratory.

Proof of initial testing validation in which positive and negative HER2 categories are 95% concordant with alternative validated method or same validated method for HER2.

Ongoing validation should be done biannually.

## Optimal internal QA procedures

### Recommendation:

Initial test validation.

Ongoing quality control and equipment maintenance.

Initial and ongoing laboratory personnel training and competency assessment.

Use of standardized operating procedures including routine use of control materials.

Revalidation of procedure if changed.

Ongoing competency assessment and education of pathologists.

## Optimal external proficiency assessment

### Recommendation:

Participation in external proficiency testing programs with at least two testing events (mailings)/year.

Satisfactory performance requires at least 90% correct responses on graded challenges for either test.

- Unsatisfactory performance will require laboratory to respond according to accreditation agency program requirements.

## Optimal laboratory accreditation

### Recommendation:

Onsite inspection every other year with annual requirement for self-inspection.

- Reviews laboratory validation, procedures, QA results and processes, results and reports.
- Unsatisfactory performance results in suspension of laboratory testing for HER2 for that method.