HER2 TESTING IN BREAST CANCER

Clinical Practice Guideline Update

American Society of Clinical Oncology / College of American Pathologists
Introduction & Context


• The Update Committee was convened in 2012.

• Purpose of HER2 testing is to identify patients who could benefit from effective HER2-targeted therapies.

• Between 15 and 20 percent of all newly diagnosed breast cancers are HER2 positive.
Introduction

• The 2007 guideline created a diagnostic algorithm for HER2 testing by acceptable testing methods of immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) and defined acceptable specimen handling methods.

• The 2013 Guideline Update modifies the diagnostic algorithm to account for specimen and genomic heterogeneity, adds bright-field ISH as an acceptable method of testing, discusses challenging scenarios, and emphasizes the need for clinicopathologic correlation and the critical need for enhanced communication between pathologists and oncologists.

• Guideline impact was emphasized by the remarkable uptake of labs participating in CAP proficiency testing since publication of 2007 Guideline
ASCO/CAP Guideline Methodology: Systematic Review

• Update Committee reviewed relevant data and revised recommendations
• Literature Search Strategy
  – MEDLINE
  – Cochrane Collaboration Library
• Date parameters: January 2006- January 2013
• Extensive external review of draft
• Approved by ASCO Clinical Practice Guidelines Committee and CAP Committees

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The Bottom Line

• Intervention
  – Recommendations for HER2 testing in breast cancer

• Target Audience
  – Medical oncologists, pathologists, and surgeons

• Key Recommendations for Oncologists and Pathologists (below)

• Methods
  – Systematic review and analysis of the medical literature

• Additional Information
  – The revised recommendations and a summary of the literature and analysis are provided in guideline.
  – Data Supplements and Clinical Tools and Resources can be found at http://www.asco.org/guidelines/her2 and www.cap.org
  – Patient information is available at http://www.cancer.net

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.
Clinical Questions

1. What Is the Optimal Testing Algorithm for the Assessment of HER2 Status?

2. What Strategies Can Help Ensure Optimal Performance, Interpretation, and Reporting of Established Assays?
Key Recommendations: Oncologists
(Tables 1 and 2 in the Guideline and online Data Supplements provide more detail)

• Must request HER2 testing on every primary invasive breast cancer and on metastatic site(s) (if stage IV and if specimen available) from a patient with breast cancer to guide decision to pursue HER2-targeted therapy. ¹

• Should recommend HER2-targeted therapy if HER2 test result is Positive and if there is no apparent histopathologic discordance with HER2 testing and if clinically appropriate. ²
Key Recommendations: Oncologists

• Must delay decision to recommend HER2-targeted therapy if initial HER2 test result is Equivocal. Reflex testing should be done on the same specimen using the alternative test if initial HER2 test result Equivocal or on an alternative specimen.

• Must not recommend HER2-targeted therapy if HER2 test result Negative and if there is no apparent histopathologic discordance with HER2 testing. ³
Key Recommendations: Oncologists

- Should delay decision to recommend HER2-targeted therapy if HER2 status cannot be confirmed as positive or negative after separate HER2 tests (HER2 test result or results Equivocal). 4

- If the HER2 test result is ultimately deemed to be Equivocal, even after reflex testing with an alternative assay, the oncologist may consider HER2-targeted therapy. 5

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Key Recommendations: Pathologists

(Tables 1 and 2 in the Guideline and online Data Supplements provide more detail)

• Must ensure that at least one tumor sample from all patients with breast cancer (early-stage or metastatic disease) is tested for either HER2 protein expression with IHC assay or HER2 gene ISH assay using a validated HER2 test.

• In the US, the ASCO/CAP Guideline Update Committee preferentially recommends the use of an assay that has received FDA-approval, although a CLIA-certified lab may choose instead to use a laboratory-developed test (LDT). 6

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Key Recommendations: Pathologists

• Must report a **HER2 test result as Positive** if: (a) IHC 3+ Positive or (b) ISH Positive using either a Single Probe ISH or Dual Probe ISH. This assumes that there is no apparent histopathologic discordance observed by the pathologist.

• Must report a **HER2 test result as Equivocal** and order reflex test on the same specimen (unless the pathologist has concerns about the specimen) using the alternative test if: (a) IHC 2+ Equivocal or (b) ISH Equivocal using Single Probe ISH or Dual Probe ISH. This assumes that there is no apparent histopathologic discordance observed by the pathologist.7

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Key Recommendations: Pathologists

• Must report a **HER2 test result as Negative** if a single test (or all tests) performed in a tumor specimen show: (a) IHC 1+ Negative or IHC 0 Negative or (b) ISH Negative using Single Probe ISH or Dual Probe ISH. This assumes that there is no apparent histopathologic discordance observed by the pathologist.

• Must report a **HER2 test result as Indeterminate** if technical issues prevent one or both tests (IHC and ISH) done in a tumor specimen from being reported as positive, negative, or equivocal.

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Key Recommendations: Pathologists

- Must ensure that interpretation and reporting guidelines for HER2 testing are followed.

- Should interpret bright-field ISH on the basis of a comparison between patterns in normal breast and tumor cells, as artifactual patterns may be seen that are difficult to interpret. If tumor cell pattern is neither normal nor clearly amplified, test should be submitted for expert opinion.

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Key Recommendations: Pathologists

• Should ensure that any specimen used for HER2 testing (cytological specimens, needle biopsies, or resection specimens) begins the fixation process quickly (time to fixative within 1 hour) and is fixed in 10% neutral buffered formalin for 6 to 72 hours, and that routine processing, as well as staining or probing are done according to standardized analytically validated protocols.

• Should ensure that the laboratory conforms to standards set for CAP accreditation, or an equivalent accreditation authority, including initial test validation, ongoing internal quality assurance, ongoing external proficiency testing, and routine periodic performance monitoring.

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Key Recommendations: Pathologists

• If an apparent histopathologic discordance is observed in any HER2 testing situation the pathologist should consider ordering additional HER2 testing and conferring with the oncologist, and should document the decision-making process and results in the pathology report. As part of the HER2 testing process, the pathologist may pursue additional HER2 testing without conferring with the oncologist.

• Although categories of HER2 status by IHC or by ISH can be created that are not covered by these definitions, in practice they are uncommon and if encountered should be considered “IHC Equivocal” or “ISH Equivocal”.

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HER2 Testing IHC

HER2 testing (invasive component) by validated IHC assay

Batch controls and on-slide controls show appropriate staining

- Circumferential membrane staining that is complete, intense, and within > 10% of tumor cells*
  - IHC 3+ positive
- Circumferential membrane staining that is incomplete and/or weak/moderate and within > 10% of tumor cells*
  - IHC 2+ equivocal
- Incomplete membrane staining that is faint/barely perceptible and within > 10% of tumor cells*
  - IHC 1+ negative
- No staining is observed* or membrane staining that is incomplete and is faint/barely perceptible and within ≤ 10% of tumor cells
  - IHC 0 negative

Must order reflex test (same specimen using ISH) or order a new test (new specimen if available, using IHC or ISH)

HER2 Testing Single Probe ISH

HER2 testing (invasive component) by validated single-probe ISH assay

Batch controls and on-slide controls show appropriate hybridization

- Average HER2 copy number ≥ 6.0 signals/cell* → ISH positive
- Average HER2 copy number ≥ 4.0 and < 6.0 signals/cell* → ISH equivocal
- Average HER2 copy number < 4.0 signals/cell → ISH negative

Must order a reflex test (same specimen using dual-probe ISH or using IHC) or order a new test (new specimen if available, using ISH or IHC)

*Values are approximate and may vary depending on the assay and staining protocol.
HER2 Testing by Dual-Probe ISH

HER2 testing (invasive component) by validated dual-probe ISH assay

Batch controls and on-slide controls show appropriate hybridization

HER2/CEP17 ratio ≥ 2.0*

Average HER2 copy number ≥ 4.0 signals/cell*

ISH positive

Average HER2 copy number < 4.0 signals/cell*

ISH positive†

HER2/CEP17 ratio < 2.0

Average HER2 copy number ≥ 6.0 signals/cell*

ISH positive

Average HER2 copy number ≥ 4.0 and < 6.0 signals/cell*

ISH equivocal

Average HER2 copy number < 4.0 signals/cell

ISH negative

Must order a reflex test (same specimen using IHC), test with alternative ISH chromosome 17 probe, or order a new test (new specimen if available, ISH or IHC)


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Ongoing Efforts by CAP: Communication, Education and Evaluation

• CAP has undertaken comprehensive efforts to educate pathologists about ways to improve laboratory performance

• Live and online educational offerings
  – Follow-up surveys indicate that courses lead to changes in practice

• Scored assessments included in many courses

• Can be used to meet certification requirements

• Listing of the courses is available online at [http://www.cap.org](http://www.cap.org) via the learning portal

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Patient and Clinician Communication

• Patients, family members and/or caregivers should be educated about:
  – Results of pathology tests
  – How they are used to develop a treatment plan

• Use easily-understood language

• Ask patients to repeat back key pieces of information

• Provide written or recorded notes

• Use visual aids

• Give patients a copy of pathology report and test results

• Review results with patient

• Solicit questions

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Patient and Clinician Communication

• Explain to patients:
  – The importance of determining the biologic characteristics of breast cancer.
  – The importance of HER2 testing
  – The type of tissue used for HER2 testing
  – The types of tests used to determine HER2 status
  – The interpretation of the HER2 test results
  – The importance of retesting HER2 status in new, metastatic tumors
  – That the ASCO/CAP HER2 Testing Guideline is online

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Health Disparities

• Important to note that racial/ethnic minority patients may have limited access to optimal medical care and/or accredited pathology laboratories

• Medicaid or uninsured patients may have access to accredited pathology laboratories if receiving care in academic medical center

• Disparities clearly exist in the likelihood of receiving HER2 testing
  – Rates do not vary significantly based on socio-economic status
  – Similar testing rates between black and white women
  – Hispanic women are significantly less likely to receive testing
  – Older women and women with distant disease are less likely to receive testing
Limitations and Future Directions

• Interpretation of the literature in the field of HER2 testing is still complicated by:
  – Lack of standardization across trials in assay utilization and interpretation
  – Presence or absence of confirmatory testing
  – Local versus central laboratory testing

• FDA-approved assays have been carefully validated, but not all LDTs may have been clinically validated.
  – Complicates direct comparisons across trials and platforms
  – Could lead to over- or under-treatment with HER2-targeted therapies

• There is a gap in literature concerning patients with results reported as equivocal.

• Decision to treat with specific therapies is dichotomous, however HER2 testing results are derived from a continuous variable.

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Limitations and Future Directions

• Literature is lacking:
  – Sufficient evidence on response to HER2-targeted therapy in patients with equivocal results
  – Efficacy data in the subgroup tested with both high quality IHC and FISH and found to have a discordant result between these two tests

• If HER2 expression that does not reach the threshold for HER2-positive disease, the Update Committee urges patients to enroll, if eligible, into prospective clinical trials.

• The Update Committee also supports participation in studies evaluating other cutoffs and other technologies to optimize eligibility for HER2-targeted therapies.
# Update Committee Members

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* Steering Committee members
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Additional Resources

• The guideline is available at http://jco.ascopubs.org

• The guideline, data supplements, patient materials, and other resources are available at www.asco.org/guidelines/her2 and www.cap.org

• The patient guide is also available at http://www.cancer.net
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