

**The critical role of the surgeon in**

# **Optimal HER2 testing in invasive breast cancer**

**2007 update to ASCO/CAP recommendations**

## **Indications**

Herceptin (Trastuzumab), as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel, is indicated for the adjuvant treatment of patients with HER2-overexpressing, node-positive breast cancer.

Herceptin in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease.

Herceptin as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease.



## Surgeons and HER2 testing accuracy

- **Surgeons play a critical role in ensuring that HER2 status is accurately determined**
  - Appropriate handling and preparation of tissue samples are necessary to maintain integrity of sample for testing
  - Identification and selection of labs accredited by the College of American Pathologists (CAP) help guarantee high-quality testing
  - An understanding of testing algorithms, interpretation criteria, and reporting elements gives the surgeon essential information for reviewing and making decisions based on pathology reports
- **HER2 testing inaccuracy is a significant issue, whether IHC or FISH is used**
  - In some analyses, about 20% of HER2 tests performed in the field\* were later discordant with the result of the same specimen tested in a high-volume lab<sup>1,2</sup>
  - A number of factors can influence the accuracy of results, including the handling and processing of tissue samples that are being prepared for assay
- **To address this problem, the American Society of Clinical Oncology (ASCO) and CAP established an expert panel to develop recommendations for standardizing HER2 testing in breast cancer<sup>3,4</sup>**
  - A summary of recommendations are included in this booklet
  - Additional information and details can be found in the full recommendations, published in the *Journal of Clinical Oncology* and the *Archives of Pathology & Laboratory Medicine*<sup>3,4</sup>

\* At the primary treatment site's pathology department.

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## ASCO/CAP recommendations relevant across specialties

- The following chart highlights ways in which various specialists may use relevant elements of the recommendations:

Use of HER2 testing guidelines by specialty			
	Surgeon	Medical oncologist	Pathologist
Testing algorithm	May compare the testing algorithm used for a given specimen with the recommended algorithm		Should understand when and how it is recommended to retest samples that have equivocal test results
Testing requirements	Should use recommended techniques for tissue acquisition and length of fixation	May compare testing practices used for a given sample with the recommended requirements	Should adopt recommendations for length of fixation, controls, and cell counting
Interpretation criteria	Should understand the implications of "positive" or "negative" reported result		Should ensure that the test result is captured and interpreted in a standardized and accurate way
Reporting elements	Can look for specific testing elements that should be standardly reported, and which may be relevant for clinical decision making		Should report the recommended elements of testing
Validation/ Accreditation	May check whether the laboratory used is accredited and has validation and QA procedures in place		Should adopt internal validation and QA procedures, and maintain standards for external laboratory accreditation

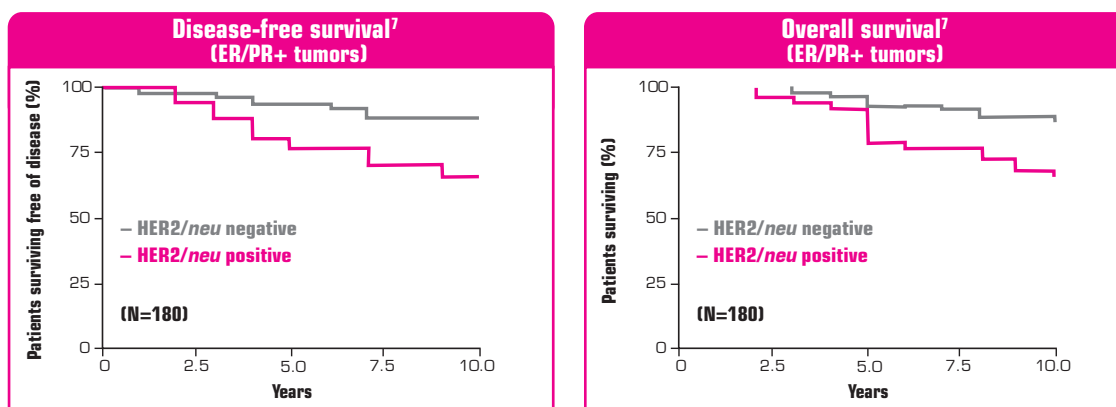
## Cooperation is key among specialists

- Cooperation among specialists is critical to help ensure accurate results and appropriate disease management
- One retrospective study demonstrated that multidisciplinary review of breast cancer patients is likely to impact management recommendations<sup>5</sup>
  - Among 149 referrals to a multidisciplinary breast cancer clinic from an outside facility, more than half (77) resulted in changes in the surgical management recommendations
  - These findings underscore the importance of a collaborative approach to pathologic interpretations and treatment decisions



## HER2 status has important implications in breast cancer, regardless of hormone-receptor status

- HER2 overexpression predicts poor results even in patients whose breast cancers overexpress hormone receptors (ER/PR+ tumors)<sup>6,7</sup>
  - Based on a 2005 clinical study by Gago et al, which included 516 patients with stage I and II tumors, HER2+ tumors are associated with significantly worse disease-free survival ( $P<0.001$ ) and overall survival than HER2-negative tumors ( $P=0.001$ )<sup>7</sup>



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**Study Design:** This prospective clinical trial included 516 consecutive patients with previously untreated stage I or stage II primary breast cancer, 180 of whom had ER/PR+ tumors. All patients received tamoxifen alone or chemotherapy plus tamoxifen. Patients were followed for 5-10 years (mean of 7.3). Immunohistochemistry of tumor biopsies was used to determine protein expression.<sup>7</sup>

- HER2 positivity may impact response to endocrine therapies, certain chemotherapies, and HER2-targeted therapies<sup>3,4</sup>
- The potential benefits of HER2-targeted agents stress the importance of correctly identifying HER2 status to guide therapeutic decision making<sup>3,4</sup>

## Optimal tissue-handling requirements<sup>3,4</sup>

- HER2 status should be determined for all cases of invasive breast cancer
- The accuracy of HER2 test results depends in part upon the quality of the tissue sample
- The following processes are recommended by ASCO/CAP to help ensure high-quality tissue samples for assays:

### Tissue fixation

- Time from tissue acquisition to fixation should be as short as possible
- Samples should be placed in sufficient volume of neutral buffered formalin
- Fixation for <6 hours or >48 hours is not recommended prior to either FISH or IHC\*
- Time to fixation and duration of fixation, if available, should be recorded for each sample

### Core needle biopsies

- When core needle biopsies are conducted, they should not be used for assays if they exhibit:
  - Edge or retraction artifact involving entire core
  - Crush artifact (thin gauge, vacuum extraction needle samples)

\*Guidelines allow for needle core biopsies to be fixed for a minimum of 1 hour, but strongly suggest longer fixation times.

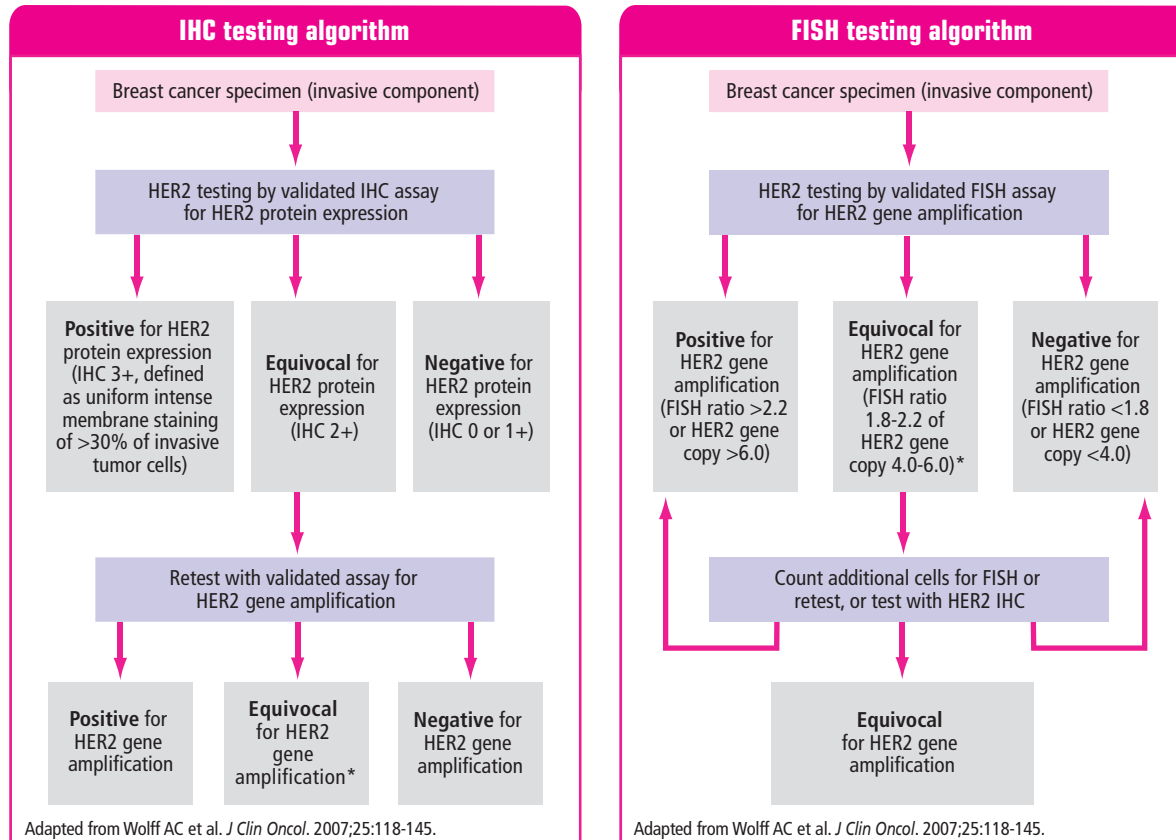
## Accreditation and quality assurance<sup>3,4</sup>

- Tissue samples to be tested for HER2 status should be sent to a laboratory that:
  - Is accredited by CAP, **or**
  - Meets the accreditation and proficiency requirements detailed in the full guidelines
- Achievement or maintenance of CAP accreditation now requires laboratories to demonstrate proficiency in the specific type of testing being offered
- Details of accreditation and validation recommendations can be found in the full guidelines, published in the *Journal of Clinical Oncology* and the *Archives of Pathology & Laboratory Medicine*<sup>3,4</sup>



## Algorithms for HER2 testing<sup>3,4</sup>

- The surgeon may wish to confirm that a final “positive” or “negative” HER2 result was achieved using the approved testing algorithms for IHC and FISH



- The ASCO/CAP guidelines have redefined “equivocal” FISH results as a HER2/CEP17 FISH ratio between 1.8 and 2.2
- However, since patients with FISH scores of 2.0-2.2 were eligible for the adjuvant trastuzumab trials, the guidelines conclude that the available data **do not support excluding patients** with these results from receiving Herceptin

## Reporting elements<sup>3,4</sup>

- Surgeons rely upon pathology reports to accurately diagnose cancer and decide upon appropriate treatment
- The ASCO/CAP testing guidelines recommend standardized information that should be available to the clinician for these purposes

### Key elements of reporting

- Patient and physician identification
  - Date of test
  - Specimen identification, site, type, and fixative type
  - Time to fixation and duration of fixation
  - Details of the method used (including whether it is FDA-approved), the controls, and the adequacy of the sample for evaluation
  - Quantitative results and pathologist’s interpretation of results
- Details of reporting recommendations can be found in the full guidelines, published in the *Journal of Clinical Oncology* and the *Archives of Pathology & Laboratory Medicine*<sup>3,4</sup>

**Note:** It is important to note that guidelines cannot always account for individual variation among patients. Guidelines are not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same result. Accordingly, ASCO considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient’s individual circumstances.

### **Boxed WARNINGS and Additional Important Safety Information**

**Herceptin administration can result in left ventricular dysfunction and congestive heart failure (CHF).** The incidence and severity of left ventricular cardiac dysfunction/CHF were highest in patients who received Herceptin concurrently with anthracycline-containing chemotherapy regimens. Discontinue Herceptin treatment in patients receiving adjuvant therapy for breast cancer and strongly consider discontinuation of Herceptin in patients with metastatic breast cancer who develop a clinically significant decrease in left ventricular function.

Patients receiving Herceptin should undergo frequent monitoring for deteriorating left ventricular function. More frequent monitoring should be employed in patients with preexisting cardiac dysfunction receiving Herceptin. Monitoring will not identify all patients who will develop cardiac dysfunction.

**Serious infusion reactions and pulmonary toxicity have occurred;** rarely these have been fatal. In most cases, symptoms occurred during or within 24 hours of administration of Herceptin. Herceptin infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of Herceptin should be strongly considered for infusion reactions manifesting as anaphylaxis, angioedema, pneumonitis, or acute respiratory distress syndrome.

Exacerbation of chemotherapy-induced neutropenia has also occurred.

The most common adverse reactions associated with Herceptin use were fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia.

Please see enclosed full Prescribing Information, including **Boxed WARNINGS**, for additional important safety information.

**References:** **1.** Paik S, Bryant J, Tan-Chiu E, et al. Real-world performance of HER2 testing—National Surgical Adjuvant Breast and Bowel Project experience. *J Natl Cancer Inst.* 2002;94:852-854. **2.** Roche PC, Suman VJ, Jenkins RB, et al. Concordance between local and central laboratory HER2 testing in the Breast Intergroup trial N9831. *J Natl Cancer Inst.* 2002;94:855-857. **3.** Wolff AC, Hammond EH, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer. *J Clin Oncol.* 2007;25:118-145. **4.** Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer. *Arch Pathol Lab Med.* 2007;131:18-43. **5.** Newman EA, Guest AB, Helvie MA, et al. Changes in surgical management resulting from case review at a breast cancer multidisciplinary tumor board. *Cancer.* 2006;107(10):2346-2351. **6.** Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/*neu* oncogene. *Science.* 1987;235:177-182. **7.** Gago FE, Fanelli MA, Ciocca DR. Co-expression of steroid hormone receptors (estrogen receptor alpha and/or progesterone receptors) and HER2/*neu* (c-erbB-2) in breast cancer: clinical outcome following tamoxifen-based adjuvant therapy. *J Steroid Biochem Mol Biol.* 2006;98:36-40.

[www.herceptin.com](http://www.herceptin.com)

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