

# 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 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.

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.



## Boxed WARNINGS and Additional Important Safety Information<sup>6</sup>

### 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 pre-existing 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**.

**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. 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. 6. Herceptin Prescribing Information. Genentech, Inc. November 2006.

## Oncologists play an important role in HER2 testing accuracy

- 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 determined to be incorrect<sup>†1,2</sup>
- To address this problem, the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (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*
- ASCO/CAP recommendations recognize the critical role of oncologists in HER2 testing accuracy<sup>3,4</sup>
  - Review of pathology reports
  - Confirmation of laboratory quality assurance, based on ASCO/CAP accreditation and validation requirements

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## ASCO/CAP recommendations relevant across specialties

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

Relevance of HER2 testing guidelines by specialty			
	Medical oncologist	Surgeon	Pathologist
<b>Testing algorithms</b>	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 with equivocal test results
<b>Testing requirements</b>	May compare testing practices used for a given sample with the recommended requirements	Should utilize recommended techniques for tissue acquisition and length of fixation	Should adopt recommendations for length of fixation, controls, and cell counting
<b>Interpretation criteria</b>	Understand the implications of "positive" or "negative" reported result		Should ensure that test result is captured and interpreted in a standardized and accurate way
<b>Reporting elements</b>	Can look for specific testing elements that should be standardly reported, and may be relevant for clinical decision making		Should report the recommended elements of testing
<b>Validation/ accreditation</b>	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

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

†Result discordant with result of same specimen tested in a high-volume central laboratory.

### Important Safety Information

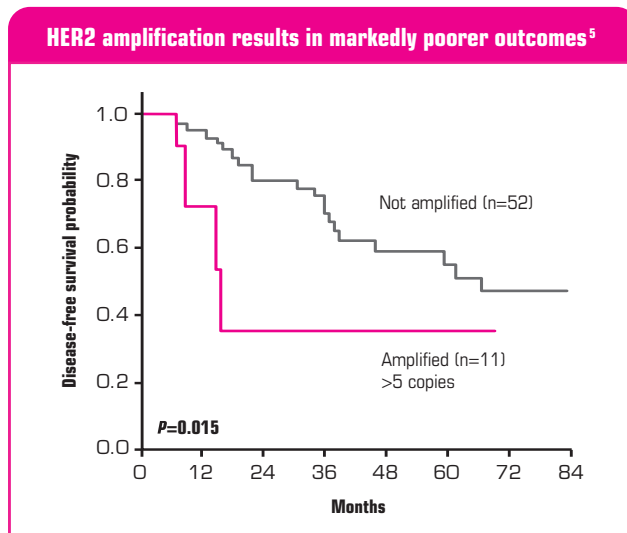
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## HER2 status has important implications in breast cancer

- HER2 positivity is associated with poor prognosis (higher rate of recurrence and mortality in patients newly diagnosed with breast cancer)<sup>3-5</sup>



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- HER2 positivity may impact response to endocrine therapies, certain chemotherapies, and HER2-targeted therapies<sup>3,4</sup>

- Herceptin has been proven effective in HER2+ breast cancer in the adjuvant and metastatic settings<sup>3,4,6</sup>
  - In the adjuvant setting, for patients with HER2+, node-positive disease, chemotherapy plus 52 weeks of Herceptin significantly improved disease-free survival, reducing the risk of disease recurrence by 52%<sup>6</sup>
  - In the metastatic setting, Herceptin is the only HER2-targeted therapy proven to extend survival in patients with HER2+ breast cancer<sup>6</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>

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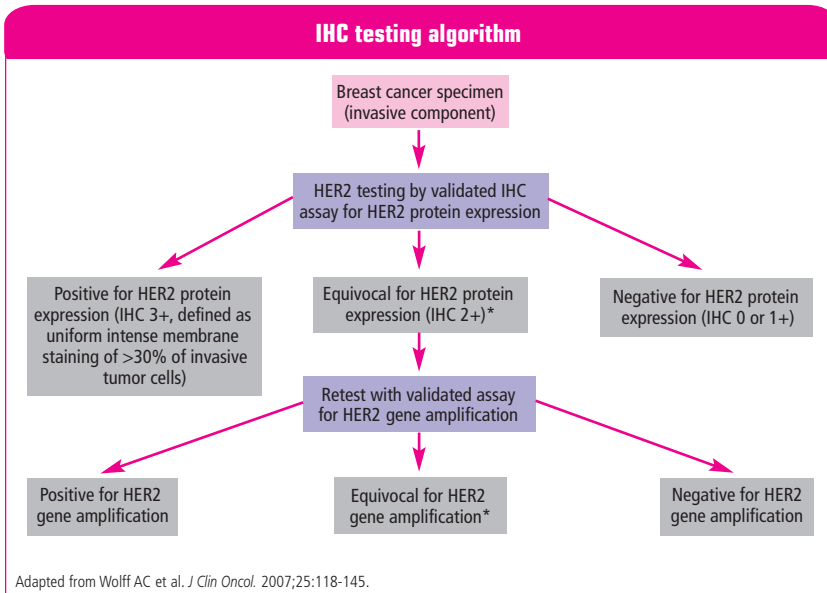
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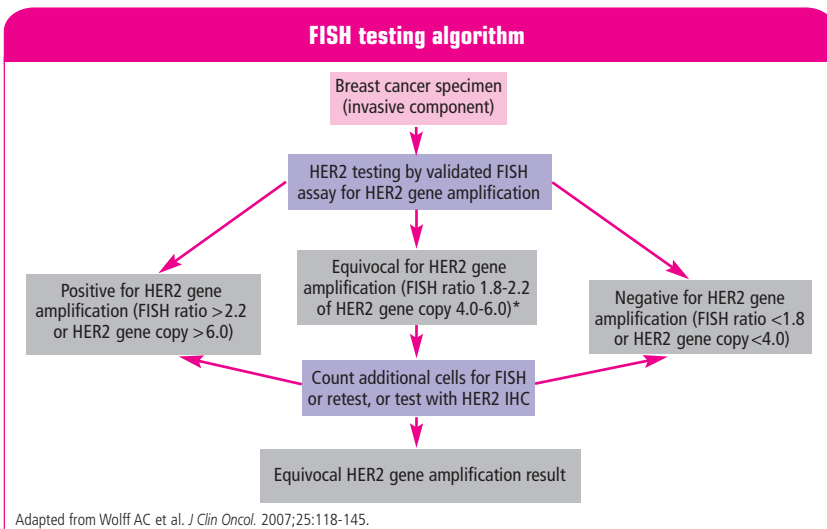
# Algorithms for HER2 testing<sup>3,4</sup>

- HER2 status should be determined for all cases of invasive breast cancer<sup>3,4</sup>



\*Patients with HER2/CEP17 ratio  $\geq 2.0$  were eligible for the adjuvant trastuzumab trials.

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

- Oncologists 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 include:
  - 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*

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

- HER2 testing should be conducted at 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*

**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.

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