

Guideline Summary: American Society of Clinical Oncology/ College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor HER2 Testing in Breast Cancer

Context

The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) collaborated to develop an evidence-based guideline for optimal human epidermal growth factor receptor 2 (HER2; also sometimes referred to as *c-neu* or *c-erbB-2*) testing performance in invasive breast cancer (*J Clin Oncol* 25:118-145, 2007). The ASCO/CAP Expert Panel, composed of a range of experts in clinical medicine, pathology, and health services research, conducted a systematic review of the literature to formulate recommendations for improving the accuracy of HER2 testing and its utility as a predictive marker.

Overview

HER2 amplification occurs in approximately 18% to 20% of breast cancers. Overexpression of HER2 is associated with relevant clinical outcomes in patients with invasive breast cancer. HER2 positivity is often incorporated into prognostic decision-making regarding adjuvant systemic therapy. HER2 status is also predictive for relative resistance and response to certain endocrine therapies and chemotherapy drugs. The ASCO/CAP Expert Panel addresses quality assurance measures and recommends specific methodology to improve HER2 testing accuracy. The Panel recommends that HER2 status be determined for all invasive breast cancers.

Methodology

The ASCO/CAP Expert Panel used evidence from January 1987 thru February 2006 to form the evidence base for recommendation consensus. Databases searched included MEDLINE, PreMEDLINE, and the Cochrane Collaboration Library. The Panel also reviewed abstracts presented at ASCO and CAP from 2000 to 2005 and the San Antonio Breast Cancer Symposium from 2003 to 2005. In addition to a broad international comprehensive medical and research specialty representation on the Panel, representatives from the US Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS) served as ex-officio panel members. Select external experts reviewed the guideline, and it was approved by ASCO's Board of Directors and CAP's Board of Governors.

Discussion

HER2 Status and Trastuzumab

Trastuzumab, an anti-HER2 therapy, is a humanized monoclonal antibody that improves response rates, time to progression, and survival when used following or combined

with chemotherapy in metastatic breast cancer. Approved by the US FDA in 1998 for the treatment of metastatic disease, adjuvant trastuzumab has now been shown in five randomized trials to substantially reduce the risk of recurrence (and in some cases the risk of death) in patients with high-risk, early-stage breast cancer that overexpresses HER2. The current recommended schedule for adjuvant trastuzumab at 12 months is associated with US costs ranging from \$70,000 to \$110,000. Trastuzumab has also been shown in prospective randomized adjuvant trials to correlate with asymptomatic cardiac dysfunction (5% to 15% of patients) and symptomatic congestive heart failure (2% to 4% of patients). Prospective substudies of adjuvant randomized trials demonstrated that as many as 15% to 20% of the HER2 assays performed in the field may be incorrect when the same specimen was re-evaluated in a high-volume, central laboratory. The ASCO/CAP Expert Panel found that HER2 testing inaccuracies, coupled with trastuzumab costs and associated cardiac toxicity, demand accurate HER2 testing.

FDA-Approved Assays and HER2 Testing

Several assays have been used for tissue-based HER2 determination. These assays include immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), bright field in situ hybridization, either as "home brews" (ie, modifications of existing assays or new assays developed by individual pathology laboratories) or commercial assays approved in the United States by the FDA. Certain FISH and IHC tests are the only assays approved by the US FDA. Still, analyses of prospective randomized adjuvant trials of trastuzumab illustrated that testing algorithms for HER2 had not been standardized and were developed somewhat arbitrarily. Therefore, the Panel strongly recommends validation of laboratory assays or modifications, use of standardized operating procedures, and compliance with new testing criteria to be monitored with the use of stringent laboratory accreditation standards and ongoing proficiency testing.

In accordance with the guideline recommendations, CAP-accredited laboratories (or those that meet the accreditation requirements specified in the guideline) that test for HER2 are required to participate in proficiency testing. Oncologists are encouraged to verify the accreditation status of laboratories used to test for HER2 overexpression, as well as confirm standardized reporting elements for IHC and/or FISH when reviewing HER2 test assessments. Table 1 presents standardized reporting elements.

HER2 Test Results

The HER2 testing guideline provides recommendations to specify HER2 testing methodologies and provide quality assurance measures to better inform clinical decision-making. HER2 testing results are categorized as positive, equivocal, or negative. It is critical that HER2 analyses be performed using the invasive component of the breast cancer, as HER2 overexpression is frequently observed in in situ tumors. While there is no gold standard for comparison of

HER2 assays to perfectly forecast anti-HER2 therapy benefit, the Panel agrees on the definitions presented in Table 2 for analysis of HER2. The “equivocal” category is new and calls for additional testing. FISH analysis should be used to confirm equivocal IHC samples. Equivocal FISH samples should be confirmed through additional cell counts or by repeating the FISH test. If additional FISH analysis proves equivocal, the Panel recommends confirmatory IHC.

Table 1. Reporting Elements for IHC and FISH

IHC/FISH shared elements
Patient identification information
Physician identification
Date of service
Specimen identification (case and block No.)
Specimen site and type
Specimen fixative type
Time to fixation (if available)
Duration of fixation (if available)
Method used (specifics test/vendor and if FDA-approved)
Image analysis method (if used)
Adequacy of sample for evaluation (adequate No. of invasive tumor cells present)
IHC-specific elements
Antibody clone/vendor
Controls (high protein expression, low-level protein expression, negative protein expression, internal)
Results
• Percentage of invasive tumor cells exhibiting complete membrane staining
• Uniformity of staining: present/absent
• Homogenous, dark circumferential pattern: present/absent
Interpretation: Positive (for HER2 protein expression), equivocal (FISH will be done and reported), negative (for HER2 protein expression), not interpretable.
FISH-specific elements
Probe(s) identification
Controls (amplified, equivocal, and nonamplified, internal)
Results
• No. of invasive tumor cells counted
• No. of observers
• Average No. of <i>HER2</i> signals/nucleus or tile
• Average No. of CEP 17 chromosome probes/nucleus or tile
• Ratio of average <i>HER2</i> signals/CEP 17 probe signals
Interpretation: Positive (amplified), equivocal, negative (not amplified), not interpretable. If IHC is being done because of problems with assay or results, this should also be indicated.

NOTE. If an FDA-approved method is used, it should be stated. If the FDA-approved method has been modified, a statement in the report should be included indicating what modifications were made and that the changes have been validated. If the test is not FDA-approved or if an FDA-approved test has been modified, a clear statement must be made that the laboratory reporting the results take responsibility for test performance.

Abbreviations: IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; CEP 17, centromeric chromosome 17–specific probe. Tile is unit used for image system counting.

Table 2. HER2 Testing Results

	Testing Method	
	IHC HER2 Protein Expression	FISH HER2 Gene Amplification
Positive	3+*	HER2/CEP 17 ratio >2.2 or Average HER2 gene copy number >6†
Equivocal	2+	HER2/CEP 17 ratio of 1.8-2.2 or Average HER2 gene copy number 4-6†
Negative	0-1+	HER2/CEP 17 ratio <1.8 or Average HER2 gene copy number <4†

NOTE. Definitions depend on laboratory documentation of the following elements: (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 question-and-answer procedures; (3) participation in external proficiency testing; and (4) current accreditation by valid accrediting agency.

Abbreviations: IHC, immunohistochemistry; HER2, human epidermal growth factor receptor 2; FISH, fluorescence in situ hybridization; CEP 17, centromeric chromosome 17-specific probe.

* Defined as uniform intense membrane staining of >30% of invasive tumor cells.

† Signals/nucleus for those test systems without an internal central probe.

Additional Resources

Full-text versions of the guideline recommendations were published in the January 1, 2007, issue of the *Journal of Clinical Oncology* (www.jco.org; *J Clin Oncol* 25:118-145, 2007) and the January 1, 2007, issue of *Archives of Pathology and Laboratory Medicine* (www.cap.org). Additional resources, including a list of HER2 test reporting elements, summary slide set, and a patient guide, can be accessed at www.asco.org/guidelines/her2. The HER2 patient guide is also available on the PLWC Web site, at www.plwc.org/patientguides.

It is important to realize that many management questions have not been comprehensively addressed in randomized trials, and guidelines cannot always account for individual variation among patients. A guideline is 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 results.

Accordingly, ASCO considers adherence to this guideline to be voluntary, with ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.

The ASCO/CAP Guideline Recommendations for HER2 Testing in Breast Cancer were developed and written by Antonio C. Wolff, M. Elizabeth H. Hammond, Jared N. Schwartz, Karen L. Hagerty, D. Craig Allred, Richard J. Cote, Mitchell Dowsett, Patrick L. Fitzgibbons, Wedad Hanna, Amy Langer, Lisa M. McShane, Soonmyung Paik, Mark D. Pegram, Edith A. Perez, Michael F. Press, Anthony Rhodes, Catharine Sturgeon, Sheila Taube, Raymond Tubbs, Gail H. Vance, Marc van de Vijver, Thomas M. Wheeler, and Daniel F. Hayes.

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