Complete Summary

GUIDELINE TITLE

American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer.

BIBLIOGRAPHIC SOURCE(S)

Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, Dowsett M, Fitzgibbons PL, Hanna WM, Langer A, McShane LM, Paik S, Pegram MD, Perez EA, Press MF, Rhodes A, Sturgeon C, Taube SE, Tubbs R, Vance GH, van de Vijver M, Wheeler TM, Hayes DF, American Society of Clinical Oncology, College of American Pathologists. 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 Jan 1;25(1):118-45. [89 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Breast cancer

GUIDELINE CATEGORY

Diagnosis
Evaluation
Technology Assessment

CLINICAL SPECIALTY

Oncology
Pathology

INTENDED USERS

Clinical Laboratory Personnel
Physicians

GUIDELINE OBJECTIVE(S)

To improve the accuracy of human epidermal growth factor receptor 2 (HER2) testing in invasive breast cancer and its utility as a predictive marker

TARGET POPULATION

Patients with invasive breast cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. Human epidermal growth factor receptor 2 (HER2) testing in breast cancer
    - Immunohistochemistry
    - Fluorescent in situ hybridization (FISH)
2. Tissue handling requirements
3. Internal validation procedure
4. Quality assurance procedures
5. External proficiency assessment
6. Laboratory accreditation

MAJOR OUTCOMES CONSIDERED

- Human epidermal growth factor receptor 2 (HER2) status and benefit from anti-HER2 therapy
- Positive predictive value and negative predictive value of fluorescent in situ hybridization and immunohistochemistry to determine HER2 status, alone and in combination and concordance across platforms
- Accuracy in determining HER2 status, sensitivity, and specificity of specific tests

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The following electronic databases were searched from January 1987 through February 2006: MEDLINE, PreMEDLINE, and the Cochrane Collaboration Library. In addition, abstracts presented at American Society of Clinical Oncology (ASCO) or College of American Pathologists (CAP) from 2000 to 2005 and at the San Antonio Breast Cancer Symposium from 2003 to 2005 were identified. Results were supplemented with hand searching of selected reviews and personal files. The following MeSH terms were used in a MEDLINE search: "immunohistochemistry," "in situ hybridization, fluorescence," "genes, erbB2," "receptor, erbB2," "receptor, epidermal growth factor," "breast neoplasms," and the substance name "epidermal growth factor receptor-*neu* receptor." The search was expanded by the addition of the following text words, in varying combinations: immunohistochemistry, immunocytochemistry, "IHC," fluorescence in situ hybridization, "FISH," chromogenic hybridization, "CISH," gold-facilitated hybridization, autometallographic, bright field, "GOLDFISH," HER2, erbB2, breast cancer, and breast tumor. All searches were limited to the English language.

Study design was not limited to randomized controlled trials, but was expanded to include any study type, including cohort designs, case series, evaluation studies, comparative studies, and prospective studies. Also included were testing guidelines and proficiency strategies of various United States and international organizations. Letters, commentaries, and editorials were reviewed for any new information. Case reports were excluded.

Articles were selected for inclusion in the systematic review of the evidence if they met the following criteria: (1) the study compared, prospectively or retrospectively, the negative predictive value (NPV) or positive predictive value (PPV) of fluorescent in situ hybridization (FISH) or immunohistochemistry (IHC); the study described technical comparisons across various assay platforms; the study examined potential testing algorithms for human epidermal growth factor receptor 2 (HER2) testing; or the study examined the correlation of HER2 status in primary versus metastatic tumors from the same patients; and (2) the study population consisted of patients with a diagnosis of invasive breast cancer; and (3) the primary outcomes included the PPV and NPV of FISH and IHC to determine HER2 status, alone and in combination; concordance across platforms; accuracy in determining HER2 status and benefit from anti-HER2 therapy, sensitivity, and specificity of specific tests. Consideration was given to studies that directly compared results across assay platforms.

The panel reviewed the results of randomized controlled trials in breast cancer testing anti-human epidermal growth factor receptor 2 (HER2) therapies like trastuzumab and lapatinib. The panel also reviewed unblinded trials comparing various testing methods, describing test characteristics, and defining strategies for quality assurance of testing in the literature. Individuals representing regulatory agencies (Centers for Medicare and Medicaid Services and US Food and Drug Administration) also provided information about the regulatory framework. Individuals involved with quality assurance in the United States (CAP), Great Britain, and Canada (Province of Ontario) also provided information about

programs to measure and improve HER2 testing. Survey data from the maker of trastuzumab (Genentech) was also evaluated as well as testimony provided by testing manufacturers (Ventana, Dako, Abbott) and large clinical laboratories (Clarient, Mayo Medical Labs, Phenopath, Quest, and US Labs) to define the current status of training and testing for HER2. This information was used to help the panel define the best algorithm for testing, specify testing requirements and exclusions, and the necessary quality assurance monitoring that will make the testing less variable and more accurate.

American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) expert panel literature review and analysis. An initial abstract screen was performed by ASCO staff. The ASCO/CAP panel reviewed all remaining potentially relevant abstracts identified in the original literature searches to select studies pertinent to its deliberations. Two panel members independently reviewed each abstract for its relevance to the clinical questions, and disagreements were resolved by third-party review. Full-text articles were then reviewed for all selected abstracts. Evidence tables were developed based on selected studies that met the criteria for inclusion.

NUMBER OF SOURCE DOCUMENTS

125

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The entire panel met in March 2006; additional work on the guideline was completed through electronic mail and teleconferences of the panel. The purposes of the panel meeting were to refine the questions addressed by the guideline and

to make writing assignments for the respective sections. All members of the panel participated in the preparation of the draft guideline.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The draft guideline was disseminated for review by the entire panel. Feedback from external reviewers was also solicited. The content of the guideline and the manuscript were reviewed and approved by the American Society of Clinical Oncology (ASCO) Health Services Committee (HSC) and board of directors and by the College of American Pathologists (CAP) Council on Scientific Affairs and board of governors before dissemination.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Optimal algorithm for human HER2 testing	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 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	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 (see Table 10 in the original guideline document)
Optimal IHC testing requirements	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 (see Table 9 in the original guideline document)
Optimal tissue handling requirements	Time from tissue acquisition to fixation should be as short as possible; samples for HER2 testing are fixed in neutral buffered formalin for 6 to 48 hours; samples should be sliced at 5 to 10 mm intervals after appropriate gross inspection and margins

	designation and placed in sufficient volume of neutral buffered formalin Sections should ideally not be used for HER2 testing if cut > 6 weeks earlier; this may vary with primary fixation or storage conditions Time to fixation and duration of fixation if available should be recorded for each sample
Optimal internal validation procedure	Validation of test must be done before test is offered Initial test validation requires 25 to 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	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	Participation in external proficiency testing program 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	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

Abbreviations: HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescent in situ hybridization; QA, quality assurance

CLINICAL ALGORITHM(S)

Algorithms are provided in the original guideline document for:

- Immunohistochemistry (IHC)
- Fluorescent in situ hybridization (FISH)

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The evidence supporting each recommendation is presented in the original guideline document under "Review of Relevant Literature." In general, the literature review supporting these recommendations centered on consensus conferences held in the United States, single institution studies, experience from reference laboratories, international reports, regulations currently in force in the United States (Clinical Laboratory Improvement Amendment [CLIA] 88 and US Food and Drug Administration regulations), and expert consensus at the panel meeting.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Improved accuracy of human epidermal growth factor receptor 2 (HER2) testing in invasive breast cancer and its utility as a predictive marker

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Whether in the context of trastuzumab clinical trials or of studies comparing human epidermal growth factor receptor 2 (HER2) testing platforms, interpretation of the literature in the field of HER2 testing is complicated by a lack of standardization across trials in assay utilization and interpretation, presence or absence of confirmatory testing, and local versus central laboratory testing, among other considerations. Testing algorithms for HER2 were somewhat arbitrarily developed and assays used within algorithms have not always been standardized. While some assays have been carefully validated, others, especially the "home brew assays" have not, which complicates direct comparisons across trials and platforms, and we maintain

this situation leads to either over- or undertreatment of a substantial percentage of patients with breast cancer.

- In addition to published studies, the panel also considered previous guidelines and position statements from national and international professional organizations. Most of these earlier guidelines simply stated that HER2 testing should be performed, without addressing specific methodology, quality control, or associations with clinical outcomes. Guidelines have also emphasized the need for individual laboratories to document their own concordance experience of fluorescent in situ hybridization (FISH) versus immunohistochemistry (IHC) (90% for IHC 0 and 3+, and 95% for IHC 1+) before limiting reflex FISH testing only to IHC 2+ results. The guidelines considered were developed before the publication of the adjuvant trastuzumab data, and thus these concordance requirement parameters were set taking into account the palliative role of trastuzumab, and not the survival advantage shown in the adjuvant trials. Finally, other organizations have recommended algorithms based on best available data, which in fact have been quite sparse. It should be noted that testing algorithms described in existing guidelines assume a high level of correlation between IHC and FISH assays, which the existing literature shows may be unfounded.
- An important gap in the literature identified by the panel concerns those patients with test results in the intermediate or equivocal range. The decision to treat with specific therapies like trastuzumab is by necessity dichotomous (yes or no). However, HER2 test results are derived from a continuous variable, which can be expected to lead to some results falling into a gray area. Adding to this confusion is the fact that there is significant variation in the intermediate ranges for both the IHC and FISH assays. The literature is lacking in this subgroup of patients with intermediate results, and there are also limited efficacy data in the subgroup tested with both high-quality IHC and FISH and found to have a discordant result. Patients with such results constitute poorly studied subgroups with less confidence in the scores and actual benefit from trastuzumab therapy. As these patient subgroups (and number of events) found within each of the individual adjuvant transtuzumab trials are relatively small, we urge those principal investigators to pool their data for a joint analysis to attempt to address some of these questions.
- It is important to emphasize that guidelines and technology assessments cannot always account for individual variation among patients. They 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, the American Society of Clinical Oncology (ASCO) considers adherence to this guideline assessment to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, this guideline describes the use of procedures and therapies in clinical practice; it cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment is needed.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

To be effective, these recommendations must be widely communicated to the medical community and to patients both by educational efforts and by modifying the regulatory oversight of laboratories doing human epidermal growth factor receptor 2 (HER2) testing. We recommend coordinated educational efforts by both College of American Pathologists (CAP) and American Society of Clinical Oncology (ASCO) to provide such education and coordinate standardized review criteria among all agencies performing laboratory accreditation. In addition, CAP will periodically publish the aggregate results of the proficiency testing results to make the oncology community aware of the improvements resulting from this strategy.

Educational Requirements and Communication Strategies

For this guideline to be effectively implemented by laboratories anywhere in the world, there will need to be effective and widespread educational efforts of pathologists, oncologists, patients, and advocacy groups. CAP will offer online and live educational sessions about clinical necessity, testing requirements, test interpretation guidelines, and methods by which acceptable performance will be measured through laboratory accreditation and proficiency testing, and organizations in other parts of the world could play a similar role. ASCO will create education materials for oncologists and patients about how laboratory quality can be evaluated through review of reports and laboratory quality assurance activities. Pathologists must actively monitor the quality of their test procedures and oncologists on behalf of their patients must seek assurance that laboratories providing test results are appropriately accredited. These actions should improve the consistency of testing for HER2, although quantifying this improvement will be difficult. One of the important outcomes resulting from accurate HER2 testing is to ensure that every breast cancer patient who might benefit from anti-HER2 therapy be accurately and promptly identified, while those who would not benefit be spared a costly and potentially harmful placebo.

This guideline will be made available for review by organizations involved in laboratory accreditation and proficiency testing services in the USA. ASCO and CAP will jointly work to facilitate the dissemination of these guidelines. Efforts will be directed at enhancing the education of laboratories by requesting publication of guideline information in Morbidity and Mortality Weekly Report published by the Centers of Disease Control and Prevention. CAP will engage in significant live and online educational activities to help pathologists understand the significance of these changes in accreditation practice, beginning at the CAP annual meeting in September 2006. ASCO and CAP will provide educational opportunities (print, online, and society meetings) to educate health care professionals, patients, third party payers, and regulatory agencies. CAP will urge its members and participants in accreditation and proficiency testing programs to provide information in its reports specifying participation in laboratory accreditation. ASCO and CAP will work to coordinate these recommendations with those of other organizations, such as the National Comprehensive Cancer Network, the National Cancer Advisory Board, and patient advocacy organizations.

We are confident that these measures will improve performance of laboratories using these and future predictive testing methods. CAP will actively review results of proficiency testing and laboratory accreditation activities and periodically publish performance results. The organization will also work to include quality

monitoring activities of HER2 testing in its programs designed for ongoing quality assessment, similar to CAP's Q-tracks and Q-probes.

IMPLEMENTATION TOOLS

Chart Documentation/Checklists/Forms
Patient Resources
Personal Digital Assistant (PDA) Downloads
Slide Presentation

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, Dowsett M, Fitzgibbons PL, Hanna WM, Langer A, McShane LM, Paik S, Pegram MD, Perez EA, Press MF, Rhodes A, Sturgeon C, Taube SE, Tubbs R, Vance GH, van de Vijver M, Wheeler TM, Hayes DF, American Society of Clinical Oncology, College of American Pathologists. 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 Jan 1;25(1):118-45. [89 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007 Jan 1

GUIDELINE DEVELOPER(S)

American Society of Clinical Oncology - Medical Specialty Society
College of American Pathologists - Medical Specialty Society

SOURCE(S) OF FUNDING

American Society of Clinical Oncology

College of American Pathologists

GUIDELINE COMMITTEE

ASCO/CAP Expert Panel on Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment: N/A

Leadership: N/A

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Testimony: Michael F. Press, Genentech

Other: Raymond Tubbs, Nanoprobes

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in from the American Society of Clinical Oncology (ASCO) Web site. Also available from the College of American Pathologists (CAP) Web site.

Print copies: Available from American Society of Clinical Oncology, Cancer Policy and Clinical Affairs, 1900 Duke Street, Suite 200, Alexandria, VA 22314; E-mail: guidelines@asco.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Guideline recommendations for HER2 testing in breast cancer. Slide set. Alexandria (VA): American Society of Clinical Oncology; 2007. 25 p. See the related QualityTool summary on the Health Care Innovations Exchange Web site.
- ASCO/CAP guideline recommendations for HER2 testing in breast cancer: reporting elements for IHC and FISH. Alexandria (VA): American Society of Clinical Oncology; 2006. 1 p. See the related QualityTool summary on the Health Care Innovations Exchange Web site.

Electronic copies: Available in Portable Document Format (PDF) from the American Society of Clinical Oncology (ASCO) Web site. Also available from the College of American Pathologists (CAP) Web site.

Guidelines are available for Personal Digital Assistant (PDA) download from the ASCO Web site.

PATIENT RESOURCES

The following is available:

- ASCO patient guide: HER2 testing for breast cancer. 2006 Dec. Electronic copies available from the Cancer.Net Web site. See the related QualityTool summary on the Health Care Innovations Exchange Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the

authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI on February 21, 2007. The information was verified by the guideline developer on February 22, 2007.

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